No. 2022-1258, 2022-1307 (consolidated)

United States Court of Appeals for the Federal Circuit

JANSSEN PHARMACEUTICALS, INC. AND
JANSSEN PHARMACEUTICA NV
Plaintiffs-Appellees,

v.

TEVA PHARMACEUTICALS USA, INC. AND
MYLAN LABORATORIES LIMITED
Defendants-Appellants.

Appeals from the U.S. District Court for the District of New Jersey,
Case Nos. 2:18-CV-734-CCC-LDW and 2:19-CV-16484-CCC-LDW

APPELLANTS' OPENING BRIEF
(Non-Confidential Version)

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May 13, 2022

U.S. Patent No. 9,439,906, claims 1, 2, 8, 19 (Appx174-175, emphasis added)

1. A dosing regimen for administering paliperidone palmitate to a psychiatric patient in need of treatment for schizophrenia, schizoaffective disorder, or schizophreniform disorder comprising

(1) administering intramuscularly in the deltoid of a patient in need of treatment a first loading dose of about 150 mg-eq. of paliperidone as paliperidone palmitate formulated in a sustained release formulation on the first day of treatment;

(2) administering intramuscularly in the deltoid muscle of the patient in need of treatment a second loading dose of about 100 mg-eq. of paliperidone as paliperidone palmitate formulated in a sustained release formulation on the 6^{th} to about 10th day of treatment; and

(3) administering intramuscularly in the deltoid or gluteal muscle of the patient in need of treatment a first maintenance dose of about 25 mg-eq. to about 150 mg-eq. of paliperidone as paliperidone palmitate in a sustained release formulation a month (±7 days) after the second loading dose.

2. The dosing regimen of claim **1** wherein after administration of the first maintenance dose, subsequent maintenance doses of from about 25 mg-eq. to 150 mg-eq. are administered in the deltoid or gluteal muscle of the psychiatric patient in need of treatment at monthly (±7 days) intervals.

8. A dosing regimen for administering paliperidone palmitate to a renally impaired psychiatric patient in need of treatment for schizophrenia, schizoaffective disorder, or schizophreniform disorder comprising

(a) administering intramuscularly in the deltoid of a renally impaired psychiatric patient in need of treatment a first loading dose of from about 75 mg-eq. of paliperidone as paliperidone palmitate formulated in a sustained release formulation on the first day of treatment;

(b) administering intramuscularly in the deltoid muscle of the patient in need of treatment a second loading dose of from about 75 mg-eq. of paliperidone as paliperidone palmitate formulated in a sustained release formulation on the 6^{th} to about 10th day of treatment; and

(c) administering intramuscularly in the deltoid or gluteal muscle of the patient in need of treatment a first maintenance dose of about 25 mg-eq. to about 75 mg-eq. of paliperidone as paliperidone palmitate in a sustained release formulation a month (±7 days) after the second loading dose.

19. The dosing regimen of claims **1**, **4**, **8** or **11** wherein the sustained release depot formulation is an aqueous nanoparticle suspension consists essentially of

(a) 156 mg/ml of the paliperidone palmitate having an average particle size (d50) of from about 1600 nm to about 900 nm;

(b) 12 mg/ml of polysorbate 20;

(c) one or more buffering agents sufficient to render the composition neutral to very slightly basic (pH 8.5);

(d) 30 mg/ml of a suspending agent wherein the suspending agent is polyethylene glycol 4000; and

(f) water q.s. ad 100%.

CERTIFICATE OF INTEREST
(Teva)

1. The full name of all entities represented by us are:

Teva Pharmaceuticals, USA Inc.

2. The full names of all real parties in interest not identified in response to Question 3: N/A.

3. Parent corporations and publicly held companies that own 10% or more of the stock in the parties represented by us:

Teva Pharmaceuticals Industries, Inc.

4. The names of all law firms and attorneys who appeared for the parties now represented by us in the trial court or are expected to appear in this Court (and who have not or will not enter an appearance in this case) are:

Kirkland & Ellis LLP: Ashley Ross, Ashley Cade (no longer with Kirkland & Ellis), Gregory Springsted, Matthew Lembo (no longer with Kirkland & Ellis

Walsh Pizzi O'Reilly Falanga LLP: Liza M. Walsh, William T. Walsh, Jr., Christine I. Gannon

5. The title and number of any case known to counsel to be pending in this or any other court or agency that will directly affect or be directly affected by this court's decision in the pending appeal:

Janssen Pharmaceuticals, Inc. et al v. Pharmascience Inc. et al., 2-19-cv-21590 (D.N.J.); *Janssen Pharmaceuticals,Inc. v. Tolmar, Inc.*, 1:21-CV-1784 (D. Del.); *Janssen Pharmaceuticals, Inc. et al v. Accord Healthcare, Inc.*, 2:22-cv-00856 (D.N.J.)

6. Any information required under Fed. R. App. P. 26.1(b) (organizational victims in criminal cases) and 26.1(c) (bankruptcy case debtors and trustees). N/A.

CERTIFICATE OF INTEREST
(Mylan)

1. The full name of all entities represented by us are:

Mylan Laboratories Ltd.

2. The full names of all real parties in interest not identified in response to Question 3: N/A.

3. Parent corporations and publicly held companies that own 10% or more of the stock in the parties represented by us:

Mylan, Inc.; Viatris, Inc.

4. The names of all law firms and attorneys who appeared for the parties now represented by us in the trial court or are expected to appear in this Court (and who have not or will not enter an appearance in this case) are:

Katten Muchin Rosenman LLP: Guylaine Haché, Ph.D., Alissa Pacchioli

Saiber LLC: Arnold B. Calmann, Jeffrey Soos, Katherine A. Escanlar

5. The title and number of any case known to counsel to be pending in this or any other court or agency that will directly affect or be directly affected by this court's decision in the pending appeal:

Janssen Pharmaceuticals, Inc. et al v. Pharmascience Inc. et al., 2-19-cv-21590 (D.N.J.); *Janssen Pharmaceuticals, Inc. v. Tolmar, Inc.*, 1:21-CV-1784 (D. Del.); *Janssen Pharmaceuticals, Inc. et al v. Accord Healthcare, Inc.*, 2:22-cv-00856 (D.N.J.).

6. Any information required under Fed. R. App. P. 26.1(b) (organizational victims in criminal cases) and 26.1(c) (bankruptcy case debtors and trustees). N/A.

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Note re Confidential Material

Material redacted in the non-confidential version of this brief, and marked in the confidential version, at pages 16 and 67, describes Janssen's post-marketing data, which Janssen designated confidential under the terms of the protective order in case no. 18-CV-734.

Material redacted or marked at pages 68-69 and 78-80, concern specific measurements of Janssen and Teva products, and processes for performing those measurements, the details of which Janssen and Teva designated confidential under the terms of the protective order in case no. 18-CV-734.

To Appellants' knowledge, the foregoing material was treated as confidential during the district court proceedings and not revealed in publicly available filings or in proceedings open to the public.

TABLE OF AUTHORITIES

Cases

Statutes

Note: All quoted emphasis is added unless otherwise indicated.

STATEMENT OF RELATED CASES

No appeal in or from this action was previously before this Court or any other appellate court.

Appellees are asserting the patent at issue in this case (U.S. No. 9,439,906) against other parties in the following pending cases: *Janssen Pharmaceuticals, Inc. et al v. Pharmascience Inc. et al.*, 2-19-cv-21590 (D.N.J.); *Janssen Pharmaceuticals, Inc. v. Tolmar, Inc.*, 1:21-CV-1784 (D. Del.); and *Janssen Pharmaceuticals, Inc. v. Accord Healthcare Inc. et al.*, 2:22-CV-856 (D.N.J.). Those cases may directly affect or be directly affected by this Court's decision in this appeal.

INTRODUCTION

This case concerns Janssen's attempt to use a dosing-regimen patent to extend its monopoly over a lucrative antipsychotic drug (Invega Sustenna) by more than a decade. Janssen patented the paliperidone palmitate compound in *1993*, and obtained numerous follow-on patents disclosing formulations, injection sites, particle sizes, and dosing regimens. All but one of those patents have expired. Rather than accepting generic competition, Janssen has tried to forestall it until *2031* by listing Patent No. 9,439,906 in the Orange Book and asserting it against ANDA filers. The '906 patent's claims are obvious, a subset of claims are also indefinite, and the district court decision holding otherwise contravenes binding precedent in at least three ways.

First, obviousness compares *the claims* to what prior art teaches a person of ordinary skill in the art ("POSA"). 35 U.S.C. §103; *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 419-20 (2007) ("What matters is the objective reach of the claim."). A court errs when it reads claims narrowly for obviousness purposes and requires a patent challenger to prove obviousness of *additional unclaimed elements*. *See, e.g.*, *Canfield Sci., Inc. v. Melanoscan, LLC*, 987 F.3d 1375, 1383 (Fed. Cir. 2021); *Allergan, Inc. v.*

Apotex Inc., 754 F.3d 952, 962-63 (Fed. Cir. 2014). The district court committed that error twice over: It treated all claims as if they required safe and effective treatment of schizophrenia through "generalized" dosing regimens fit for all patient populations. And it limited renal-impairment claims to "mild" renal impairment. But the claims require no such thing. The claims do not cover a universal "method for treating schizophrenia," nor do they require safety, efficacy, or any particular result. They claim only "[a] dosing regimen for administering paliperidone palmitate to *a psychiatric patient in need of treatment* for schizophrenia." And the renal-impairment claims recite "[a] dosing regimen for…a *renally impaired* psychiatric patient," without limiting the degree of renal impairment. The district court erroneously required proof of obviousness of these unclaimed elements.

Second, *KSR* rejects the "rigid" approach of "overemphasi[zing] the importance of published articles and the explicit content of issued patents." 550 U.S. at 418. Instead, prior art must be analyzed from the perspective of a POSA, and considered for all it fairly teaches—including the "inferences and creative steps that a [POSA] would employ." *Id.* Con-

trary to *KSR*, the district court limited each piece of prior art to its explicit disclosures. Under the district court's approach, prior-art references teaching dosing concepts were ignored if they applied those concepts to a different drug. Prior-art references teaching paliperidone palmitate regimens were ignored if they did not specify injection sites, or used sites other than the shoulder (one of three standard sites). The court essentially ruled that the claims are not obvious because no individual reference anticipates.

By adding unwritten limitations to the claims and limiting the prior art to express disclosures, the district court skewed both sides of the statutory obviousness comparison in ways binding precedent rejects. The result is a judgment upholding claims that merely select from parameters that had been thoroughly explored in the prior art, which blocks generic competition for another decade.

Third, for a subset of claims, the district court ran afoul of indefiniteness precedent. For claims reciting measurements, "the existence of multiple methods leading to different results without guidance in the patent or the prosecution history as to which method should be used renders the claims indefinite." *Dow Chem. Co. v. Nova Chems. Corp. (Canada)*,

803 F.3d 620, 634 (Fed. Cir. 2015); *see also Teva Pharms. USA, Inc. v. Sandoz, Inc.*, 789 F.3d 1335, 1341 (Fed. Cir. 2015). That is undisputedly true of claims 19-21, which recite "an average particle size (d50) of from about 1600 nm to about 900 nm." The district court upheld those claims only by repeating nonresponsive arguments from Janssen's briefs. Under binding precedent, those claims are invalid.

The judgments upholding all claims as nonobvious and upholding claims 19-21 as not indefinite should be reversed or at least vacated and remanded.

STATEMENT OF THE ISSUES

1. Whether the district court erred by requiring Teva to prove obviousness of **(a)** "generalized" dosing regimens that would be safe and rapidly effective for all patient populations where the claims only require "[a] dosing regimen for administering paliperidone to *a* psychiatric patient in need of treatment" and **(b)** dosing regimens for patients with "mild" renal impairment where the relevant claims (8, 11, and dependents) recite no degree of renal impairment.

2. Whether the district court erred by limiting the prior art to its explicit content, failing to take account of the inferences and creative steps a POSA would take.

3. Whether Janssen's secondary-considerations evidence fails to support the judgment.

4. Whether the district court erred in holding that the "average particle size" element of claims 19-21 did not render those claims indefinite.

STATEMENT OF THE CASE

These consolidated appeals arise from separate actions. Appellants ("Teva" and "Mylan") filed ANDAs for generic versions of a paliperidone palmitate antipsychotic drug that Appellees ("Janssen") sell as Invega Sustenna. Janssen sued Teva and Mylan separately, asserting that the ANDAs infringed U.S. Patent No. 9,439,906. After Teva stipulated to infringement, Janssen prevailed at a bench trial on Teva's invalidity defenses. Mylan agreed to be bound by the result of the Teva action, and the district court entered judgment accordingly.

A. Schizophrenia and Antipsychotic Drug Development

Janssen's '906 patent recites dosing regimens for administering injections of paliperidone palmitate to a patient needing treatment for

schizophrenia or related disorders. Most relevant here, the claims recite two shoulder-injected loading doses (150 mg-eq. and 100 mg-eq.), followed by shoulder- or buttock-injected monthly maintenance doses (25-150 mg-eq.). Subsets of claims recite reduced doses for renally-impaired patients, and that the dose is an aqueous nanoparticle suspension.

Schizophrenia affects about 1% of the population. Appx11875-11876(1875:22-1876:7); *see* Appx16238; Appx13266, and is typically treated with antipsychotic drugs. Appx10084(22-24). Antipsychotic drugs were first approved in the 1950s. Appx11891-11893(1891:16-1893:4); Appx16238-16239. By the early 2000s, antipsychotic drugs were widespread, and development followed a pattern. After identifying an active molecule, the developer would first release an oral formulation for daily use. Then, the developer would later release a *long-acting injectable* ("LAI" or "depot") formulation. Appx10208-10209(208:1-209:4); Appx10097(17-19).

To convert an oral formulation to an LAI, developers typically link the active molecule to a fatty-acid to make an ester. *See* Appx10085-10086(85:17-86:4); Appx13248 (listing esterified antipsychotics). Following an injection, the body processes the esterified molecule slowly over

time, separating the ester and leaving the active molecule to circulate in the bloodstream. Appx10085-10086(85:17-86:4); *see* Appx10298(16-25).

Janssen's antipsychotic haloperidol followed that pattern. Janssen released a daily oral formulation in the 1960s. Appx10746(1-6); Appx11899-11900(1899:11-1900:21). Janssen then converted to an LAI form (haloperidol decanoate) in the 1980s, by linking haloperidol to a decanoate fatty-acid ester. Appx12655(14-18); Appx11892-11893(1892:16-1893:4).

B. Paliperidone Palmitate and Invega Sustenna

This case concerns Janssen's Invega Sustenna, an LAI drug. Invega Sustenna contains *paliperidone palmitate*, a fatty-acid ester of the active molecule paliperidone.

Paliperidone is a metabolite of *risperidone*, an older antipsychotic. Janssen discovered paliperidone in the 1990s, while developing risperidone drugs. Janssen first released a daily-oral risperidone drug ("Risperdal"), Appx10096(8-9); Appx10165(8-17); Appx16244, followed by an LAI using an extended-release coating ("Risperdal Consta"). Appx10097(17-23); Appx12656(3-5); Appx17911. Janssen found that

some of the risperidone metabolized into paliperidone (9-hydroxy-risperidone), Appx10210(2-7); Appx10275-10276(275:23-276:5); Appx10746(1-13); Appx13238(1:54-65); Appx10096-10097(96:12-97:16); Appx10098(6-9); Appx10208-10209(208:1-209:4); Appx16271, and that risperidone and paliperidone worked together to alleviate psychotic symptoms. Appx10166(21-24); Appx16250; Appx16271; Appx16279-16280.

Janssen patented the paliperidone compound in 1992, Appx18049; Appx18059(cl.1) (Patent No. 5,158,952); Appx12146-12147(2146:22-2147:10); Appx12660(1-11); *see* Appx13300, and paliperidone palmitate in 1993 and 2000. *See* Appx13292 (Patent No. 5,254,556, claiming "*$C_{2\text{-}20}$ alkanoic acid ester*"); Appx13239(3:56-64) (palmitate is "C_{15}"); Appx13297-13298 (Patent No. 6,077,843) (cls.1-2).

Janssen waited until 2006 to release a paliperidone drug. Janssen launched Invega ER (daily oral paliperidone) in 2006, Appx10099-10100(99:23-100:4); Appx10105(16-24); Appx10208-10209(208:1-209:4); Appx12655(4-6); Appx16209, and Invega Sustenna (LAI paliperidone palmitate) in 2009. Appx10105(19-20); Appx10173(22-24).

C. Main Prior Art

By 2007—the earliest possible priority date for the '906 patent—Janssen's patents on the paliperidone and paliperidone palmitate compounds were more than 15 years into their terms. Appx18049. Paliperidone palmitate's chemistry and pharmacology had been well-explored in Janssen's numerous follow-on patents and applications, which disclosed, *e.g.*, LAI formulations, aqueous formulations, injection sites, dosing regimens, methods of treating schizophrenia, the importance and effect of particle size, and the "therapeutic window" in which a drug's blood-plasma concentration is associated with efficacy but not with increased side effects.

To show obviousness at trial, Teva relied primarily on three references: **(1)** a Janssen patent disclosing doses and LAI formulations of paliperidone palmitate ("'544 patent"), **(2)** a Janssen application disclosing the exact formulation and doses of Janssen's Invega Sustenna product ("WO'384"), and **(3)** a published Janssen clinical protocol using loading doses of paliperidone palmitate ("'548 protocol").

1. Janssen's Patent No. 6,555,544 Disclosed Aqueous Nanoparticle Formulations, Uses, Doses, Therapeutic Window, Injections, Particle Size, and Durational Efficacy for Paliperidone Palmitate.

Janssen's '544 patent claimed aqueous-LAIs of paliperidone palmitate with particles in the nanoparticle-size range. Appx13237. The specification disclosed clinical aspects of paliperidone palmitate.

Formulation and Uses. The specification taught administering "therapeutically effective" amounts of paliperidone-palmitate formulations to treat schizophrenia and other psychotic disorders, Appx13241(8:9-17); Appx69 n.20, and disclosed a complete formulation for injection:

Formulation (w/v)	
9-hydroxyrisperidone palmitate	7.02% (4.5% 9-hydroxyrisperidone)
polysorbate 20	1.1%
sodium carboxymethyl cellulose 30 mPa.s	1%
benzyl alcohol parenteral	1.5%
disodium hydrogen phosphate anhydrous	0.9%
sodium dihydrogen phosphate monohydrate	0.6%
water q.s. ad	100%

Appx13241-13242(8:60-9:8).

Dose Amounts. The specification disclosed that therapeutic paliperidone palmitate doses "should range from about 2 to 4 mg/kg body

weight." Appx13241(8:17-20). Appx10238(238:3-15); Appx10284(284:16-21).

Therapeutic Window. The specification disclosed a "therapeutic window," *i.e.* suitable blood-plasma-concentration range, for paliperidone. Appx13238(2:43-50); Appx10285-10287(285:9-287:13); Appx11540(5-16); Appx14196. "[P]lasma levels above a minimal therapeutical concentration [(10 ng/mL)] but below a side-effect producing threshold value [(100 ng/mL)] are…basic requirements[.]"[1] Appx13238 (2:60-64); Appx10285-10287(285:9-287:13); Appx10382(3-18); Appx10764-10765(764:21-765:9); Appx11540(15-16). A routine blood test can determine whether a patient is within the therapeutic window. *See* Appx11735(16-24).

Injections. The specification discloses paliperidone palmitate formulations intended "for administration by intramuscular or subcutaneous injection." Appx13239(3:11-17).

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[1] Drug concentration is objective; efficacy is subjective. Appx10083-10084(83:2-84:18). Some patients with drug concentrations at the high end of the therapeutic window may nevertheless experience no efficacy, and some patients with low-end concentrations may nevertheless experience side effects. *See* Appx10285-10287(285:9-287:13); Appx10382(3-18); Appx11540(5-16); Appx11728-11729(1728:25-1729:6).

Effect of Particle Size. The specification discloses that paliperidone palmitate's pharmacokinetics—meaning "absorption, distribution, metabolism and excretion," Appx10291-10292(291:20-292:4)—"*depend on the particle size* to a much larger extent than previously held possible." Appx13239(3:46-55); *see* Appx10291(6-19); Appx11777(3-21); Appx13239 (3:46-55). Micronized (larger than nano-sized) particles have an undesirable "exceptionally longlasting effect in humans," Appx13239 (3:46-55); *see* Appx10291(6-19); Appx11777(3-21). To avoid that problem, the '544 specification explains, paliperidone palmitate LAIs should use nanoparticles below a certain size (4 m^2/g specific surface area, corresponding to approximately 2,000 nm average particle size). Appx13239(3:65-4:3); *see* Appx10294(2-17); Appx11522-11523(1522:22-1523:25).

Control of Particle Size. The specification further explains that particle size can be controlled using conventional milling, Appx13240(6:10-17); Appx10294(20-25); Appx11781(17-19), and provides four example formulations where different milling times yield different particle-size distributions:

Formulation	Milling Time	Particle Size (nm)			SSA
		d(10)	d(50)	d(90)	
Formulation A	0 hours	2510	6030	7640	1.3
Formulation B	4 hours	620	1380	6830	6.5
Formulation C	7 hours	520	740	1150	13.5
Formulation D	38 hours	430	520	650	>15

Appx13241(8:44-57). Higher "SSA" (specific surface area) means smaller particles, and "d()" represents percentage distributions. d(10) 2510 nm means 10% of particles are smaller than 2510 nm. *See* Appx10294-10296(294:2-295:25)

Duration of Efficacy. Finally, the '544 specification states the disclosed formulations are "therapeutically effective for at least three weeks or more, in particular about 1 month." Appx13238(2:38-43); Appx13241(8:17-19).

The '544 patent was in force from 2003 to 2018, and listed in the Orange Book for Invega Sustenna. Appx17768.

2. Janssen's International Application Disclosed Invega Sustenna's Formulation and Dosing Regimens (WO 2006/114384).

In 2006 Janssen filed an international application ("WO'384"), disclosing improvements over the '544 patent, including a process to prevent

unintended "breakdown products." Appx13301(2:4-6); Appx13302(3:4-7); Appx10300(15-22); Appx10302-10303(302:13-303:9).

WO'384 also disclosed *the exact formulation* Janssen would later use for Invega Sustenna. Appx10304-10305(304:23-305:3); *compare* Appx13316(tbl.6), *with* Appx166(15:16, tbl.2) ("Table 2 provides the formulation for the F013 formulation"); Appx10782(1-8) ("F13" formulation is "the one [Janssen] brought to the market[.]"). The district court's statement that WO'384 concerns "raw paliperidone palmitate crystals, as opposed to a final…formulation" is thus simply wrong. Appx68 n.19.

WO'384 also disclosed refined monthly dosing regimens of paliperidone palmitate. WO'384 disclosed pre-filling syringes with target dose volumes of 0.25-1.50 mL of the disclosed formulation, "depending on the dose needed." Appx13317(18:10-15); Appx10305(9-21). That range corresponds exactly to 25-150 mg-eq. paliperidone.[2] Appx10305(9-21); Appx12163(8-20).

[2] To convert *paliperidone palmitate* volume to milligram-equivalent *paliperidone*, the volume (0.25-1.5 mL) is multiplied by the paliperidone palmitate concentration (156 mg/mL) and by the ratio of the compounds' molecular weights (0.6414). Appx10306-10307(306:5-307:9).

3. Janssen's Published Phase III Clinical Study Protocol, NCT00210548, Disclosed Loading Doses of Paliperidone Palmitate.

In 2005, the NIH published a Janssen Phase III clinical study protocol, with identifier NCT00210548 (referred to as the "'548 protocol," describing Janssen's "PSY-3003" clinical study). Appx13244-13245; Appx10316(316:4-16); *see* Appx10300(23-25). Phase III studies are typically the last "phase," and meant to *confirm* safety and efficacy by testing already-successful regimens on a wider population. *See* Appx10207(5-23); Appx10316-10317(316:17-317:2); Appx10758(6-25); Appx11124(11-20); Appx11135(5-11). The '548 protocol used loading doses of paliperidone palmitate on schizophrenia patients: four equal buttock-injected doses of 50, 100, or 150 mg-eq. paliperidone, with loading doses on days 1 and 8; then maintenance doses on days 36 and 64. Appx13244; Appx10317(10-23); Appx10424-10425(424:18-425:7). All those doses are within the 25-150 mg-eq. range WO'384 disclosed. Appx10305(9-21); Appx12163(8-20).

D. Loading Doses, Injection Sites, and Reduced Doses for Renally-Impaired Patients Were Well-Known.

The '906 patent claims recite loading doses, injection sites, and—for renally-impaired patients—reduced doses. All three are basic concepts, well-known in prior art. Indeed, Janssen's post-marketing data show that [redacted] use and prescribing practices [redacted] use and prescribing practices [redacted]. Appx17903; Appx11195-11199(1195:18-1199:7).

1. Loading Doses of Antipsychotic Drugs

Loading dose is a "commonly applied principle." Appx10312(7-16); Appx10969(10-15). If the body processes a drug slowly, physicians may prescribe more of the drug to start treatment. A higher or additional "loading dose" at the outset permits the drug to reach a target concentration in the bloodstream more quickly, hastening therapeutic effect. Subsequent "maintenance doses" are to maintain a target drug concentration as opposed to increasing the concentration quickly from zero.

As noted, the '548 protocol discloses different paliperidone palmitate loading doses. §C.3, *supra*. Two articles from the early 1990s by Dr. Larry Ereshefsky were also in evidence, explored loading doses of antipsychotics, and reported positive results treating patients with loading

doses of LAI haloperidol decanoate. Appx14113-14119; Appx14129. And FDA's haloperidol label taught unequal loading doses. Appx11966-11968(1966:1-1968:16); Appx16651-16652.

2. Intramuscular Injections in the Shoulder, Buttock, or Thigh

Prior art taught three typical sites for intramuscular injections: shoulder (deltoid), buttock (gluteus), or thigh (vastus lateralis). *See* Appx14133; Appx14183; *see also* Appx10556(6-11); Appx11719(15-17). Each had well-understood tradeoffs. Shoulder injections are absorbed relatively quickly, "likely due to the increased blood flow in the deltoid muscle," Appx14134; Appx14183, and do not require patients to disrobe. Appx10324(3-11); Appx10857(15-20); Appx11180-11181(1180:18-1181:2). However, shoulder injections may be more painful than other sites and allow for less injection volume. Appx14134; Appx10398(7-12). For any intramuscular injection, "[a] needle long enough to reach deep into the muscle must be used[.]" Appx14133. The shoulder typically has less fat than the buttock and can accept a shorter needle.

A 2005 Janssen Phase I protocol and a 2006 Janssen Phase III study—both prior art—taught shoulder or buttock injections of paliperidone palmitate. Appx16204 (2005 protocol, "Intramuscular Injections of

Paliperidone Palmitate in the Arm or Buttock of Subjects With Schizophrenia"); Appx16206 (2006 study, "Paliperidone Palimitate Injected Into the Shoulder or the Buttock Muscle…."); Appx10280(1-15).

3. Reduced Doses for Renally-Impaired Patients

Finally, prior art taught that for drugs metabolized by the kidneys—including paliperidone—patients with reduced kidney function should receive reduced doses. It was known by 2007 that paliperidone is excreted mainly through the kidneys. Appx16297(¶¶6,39); Appx10328-10329(328:25-329:6); Appx11585-11586(1585:20-1586:10). Patients with reduced kidney function metabolize paliperidone more slowly, risking over-accumulating the drug if given the same dose as other patients. Appx14112; Appx10330(7-12); Appx10330-10331(330:24-331:5) (paliperidone exposure "basically doubl[es]" for renally-impaired patients). Prior art thus taught reduced paliperidone doses for renally-impaired patients. Appx10331(6-9). Janssen's labels for *Invega ER* (oral paliperidone) and Risperdal (the risperidone compound that metabolizes to paliperidone) both advise half-doses for renally-impaired patients. Appx16233; Appx10098(10-17); Appx17941-17942.

E. Janssen's Asserted '906 Patent

The '906 Patent issued in 2016 and expires in 2031. It is based on an application filed in 2008, and claims priority as early as December 2007. The priority date was contested at trial, but is not relevant on appeal. Janssen asserted claims 1-21.

1. All Claims Recite Two Shoulder-Injected Loading Doses, Then a Shoulder- or Buttock-Injected Maintenance Dose.

Claims 1, 4, 8 and 11 are independent. Claim 1 is below and on this brief's inside-front cover. It recites "[a] dosing regimen for administering paliperidone palmitate *to a psychiatric patient* in need of treatment for schizophrenia" or related disorders. The regimen comprises two shoulder-injected *loading* doses: **(1)** "about 150 mg-eq." on the first day, and **(2)** "about 100 mg-eq.…on the 6th to about 10th day," then **(3)** a shoulder- or buttock-injected "maintenance dose of about 25 mg-eq. to about 150 mg-eq.…a month (±7 days) after the second loading dose":

> **1.** A dosing regimen for administering paliperidone palmitate to *a psychiatric patient* in need of treatment for schizophrenia, schizoaffective disorder, or schizophreniform disorder comprising
>
> (1) administering intramuscularly in the deltoid of a patient in need of treatment a first loading dose of about 150 mg-eq. of paliperidone as paliperidone palmitate formulated in a sustained release formulation on the first day of treatment;

> (2) administering intramuscularly in the deltoid muscle of the patient in need of treatment a second loading dose of about 100 mg-eq. of paliperidone as paliperidone palmitate formulated in a sustained release formulation on the 6th to about 10th day of treatment; and
>
> (3) administering intramuscularly in the deltoid or gluteal muscle of the patient in need of treatment a first maintenance dose of about 25 mg-eq. to about 150 mg-eq. of paliperidone as paliperidone palmitate in a sustained release formulation a month (±7 days) after the second loading dose.

Appx174. As noted, the '548 protocol teaches the exact same loading-dose amounts (150 and 100 mg.-eq.), and WO'384 teaches the exact same range of claimed maintenance doses (25-150 mg-eq.).

All other independent claims recite similar regimens. Claim 4 copies claim 1, with two changes: the patient needs treatment "for psychotic disorder," and the second loading dose is "on the eighth day of treatment."

The specification has no working examples of the claimed regimens. Nor does it suggest the claimed regimens are critical or even optimal. Indeed, it states that numerous *other* "*optim[al]*" loading-dose regimens exist, such as 100 mg-eq. on days 1 and 8, or 150 mg-eq. only on day 1, followed by 25-150 mg-eq. maintenance doses *starting on day 8*. Appx170(23:16-24); *see* Appx170(23:26-24:26); Appx174(31:30-49) (describing clinical study showing doses of 25, 100, *or* 150 mg-eq. on Day 8

"were efficacious in adult subjects."). The claimed regimens merely purport to be Janssen's "discover[y]," "after extensive analysis" of *preexisting* "clinical data," of some dosing regimens, among many that Janssen expected to work. Appx160-161(4:64-5:1).

The Detailed Description contains "examples" summarizing prior studies, including a portion that *copies verbatim* from WO'384's description of making the Invega Sustenna formulation and filling vials of particular amounts. The '906 patent's tables 1, 2, and 3 of are identical to WO'384's tables 5, 6, and 7. *Compare* Appx13315-13317(tbls.5-7), *with* Appx165-166(tbls.1-3); *see also* Appx12136(16-19); Appx10552(14-23); Appx10555(5-8).

2. Claims 8, 11, and Dependents Recite Reduced Doses for "Renally Impaired Patients."

Claims 8 and 11 copy claims 1 and 4, respectively, with three changes: **(a)** claims 8 and 11 recite "a *renally impaired* psychiatric patient," **(b)** both loading doses are reduced to 75mg-eq (from 150 and 100), and **(c)** the maintenance dose range is reduced from "about" 25 to 150 to "about 25 mg-eq. to about 75 mg-eq."

3. Claims 19-21 Recite an "Average Particle Size" Limitation.

Claims 20 and 21 depend from claim 19. Claim 19 includes the following "particle size" limitation:

> 156 mg/ml of the paliperidone palmitate having *an average particle size* (d50) of from about 1600 nm to about 900 nm.

Appx175(34:35-37). The specification incorporates by reference the prior-art '544 patent's discussion of particle size. Appx162(7:25-44) (describing '544 patent teaching "[s]uitable aqueous nano particle formulations"); *see supra* §C.1 (discussing '544 patent). Neither the '906 nor '544 patents specify which techniques or machines produce measurements within the claims. The '906 patent states only that particle size can be "measured by art-known conventional techniques, such as sedimentation field flow fractionation, photon correlation spectroscopy or disk centrifugation," and describes laser diffraction in an example.

F. District Court Proceedings

Teva and Mylan submitted ANDAs for generic versions of Invega Sustenna in 2017 and 2019, respectively. Janssen first sued Teva (D.N.J. Case 18-CV-734), then Mylan (19-CV-16484), asserting infringement of the '906 patent. The actions proceeded separately before the same judge.

Janssen asserted all claims (1-21). Teva stipulated to infringement, and the court held a bench trial on Teva's invalidity defenses. Appx1061(¶16); Appx63-64. Janssen and Teva agreed for trial purposes that claims 2, 10, 13, 20, and 21 (as claims 20 and 21 depend from claims 1 or 8)[3] were representative. Appx1061; Appx56 n.3. Relevant here, Teva contended all claims were obvious and that representative claims 20 and 21 were indefinite. After trial, the court rejected Teva's defenses. Appx54-148.

1. Obviousness (All Claims)

a. The Parties' Arguments

Teva. For obviousness, Teva relied primarily on three references—the '544 patent, WO'384, and the '548 protocol (§C, *supra*). *See* Appx1063.

The '544 patent taught all elements other than the doses (*e.g.*, administering LAI paliperidone palmitate to a schizophrenia or other psychiatric patient, aqueous nanoparticle suspensions). *Supra* §C.1. And the '548 protocol and WO'384 taught the claimed doses. *Supra* §§C.1-2. For all but the renal-impairment claims, the '548 protocol taught the exact claimed paliperidone palmitate loading doses, Appx13244, and

[3] Claims 20 and 21 depend from claim 19, which recites "The dosing regimen of claims 1, 4, 8 *or* 11 wherein…" Appx175(34:32)

WO'384 taught the exact claimed paliperidone palmitate maintenance doses, and to vary "depending on the dose needed." Appx13317(18:10-15). And for the renal-impairment claims (8, 11, and dependents), the claimed doses fell within prior-art ranges, and followed undisputed prior-art teachings to administer lower doses to renally-impaired patients of drugs like paliperidone that are cleared through the kidneys. *See supra* §D.3.

For the "particle size" claims (19-21, reciting "(d50) from about 1600 nm to about 900 nm"), WO'384 taught the claimed formulation Appx13317(18:5-8), and the '544 patent taught **(a)** particle size was a result-effective variable, Appx13239(3:46-55), **(b)** d90 below 2000nm was desirable, Appx13239(3:65-4:3), and **(c)** how to control particle size with standard milling techniques. Appx13240(6:10-17); *supra* §C.1-2.

The primary prior-art references all taught dosing regimens of LAI paliperidone palmitate, and the '906 patent simply selected from prior-art dose ranges and from three standard intramuscular-injection sites, and applied the known teaching to reduce doses of kidney-cleared drugs for renally-impaired patients. Moreover, Teva argued, there should be no significant secondary considerations because Janssen had exclusive

rights to the paliperidone and paliperidone palmitate compounds for more than a decade before the 2007 critical date. Appx110-111.

Janssen. Although all claims recite administering paliperidone palmitate "to *a* psychiatric patient" Janssen insisted that Teva must prove not only that the claimed regimens would be obvious, but that it would be obvious that such regimens would be safe and rapidly effective for all patient populations. To that end, Janssen presented days of testimony about purported difficulties developing regimens that would be safe and rapidly effective for all patient populations. And Janssen labeled the '548 protocol a "failed study" and emphasized that the publication did not disclose clinical data. Appx71-74; Appx1359-1360(¶249). Janssen also asserted several categories of purported "secondary considerations."

The district court accepted nearly all of Janssen's arguments, and issued an opinion citing heavily to Janssen's briefs.

b. The Court Distinguished Prior Part By Focusing Solely on Explicit Statements and by Treating the Claims as if They Recited "Generalized" Dosing Regimens.

The district court accepted Janssen's arguments that because Janssen internally considered the '548 protocol a "failed study," Appx70-71; Appx74, and because the protocol lacked safety or efficacy data, a

POSA would have no motivation or expectation of success modifying the disclosed doses. Appx71-72.

The court then drew four distinctions between the claims and prior art: **(1)** shoulder injections (all claims), **(2)** unequal loading doses (all but the renal-impairment claims), **(3)** reduced doses for renally-impaired patients (claims 8, 11, and dependents only), and **(4)** particle size (claims 19-21).

Shoulder injections (all claims). The court did not dispute that prior art discloses three standard intramuscular injection sites (shoulder, thigh, buttock) with known pros and cons. Nonetheless, the court faulted primary prior-art references for not *expressly* reciting shoulder injections. Appx74-75. It discounted general-reference books' discussion of injection sites because "neither discloses deltoid administration *of LAI loading doses*." Appx76. And it read the claims to require a "*generalized* dosing regimen," discounting evidence on the known advantages of shoulder injections, because that evidence concerned "deltoid administration *on an individualized basis*," not "*a generalized dosing regimen*." Appx78.

Unequal loading doses (all but renal-impairment claims). The court emphasized that the '906 patent claims recited two unequal

loading doses, in contrast to the '548 protocol's equal loading doses. Appx71. As with shoulder injections, the court treated the claims as requiring a "generalized" dosing regimen, and focused on explicit details in the prior art. Thus, although the two prior-art 1990s Ereshefsky articles taught unequal loading doses, the district court discounted them because they **(1)** concerned "individualized, rather than generalized, dosing" and were thus relevant only for "dosing patients on an individualized basis," Appx79 (marks omitted), and **(2)** applied the loading-dose teaching to a different LAI antipsychotic. *See* Appx78-79.

Doses for renally-impaired patients (Claims 8, 11, and Dependents). Claims 8 and 11 recite dosing regimens for "a renally impaired psychiatric patient." *See supra* §E.2. Citing only Janssen's brief, the district court treated the renal-impairment claims as limited to patients with "mild" renal impairment. Appx81. On that basis, the court discounted one prior-art reference because it taught reduced doses for *moderate* or *severe* renal impairment. *Id.*; *see* Appx14112. The court discounted the Invega ER label because it "concerns oral paliperidone, not injectable paliperidone palmitate." *Id.* And it discounted another prior-art reference because its *title* says "hepatic [liver] impairment," even

though the reference's specification also discusses renal impairment. Appx16293; Appx16293(¶6); Appx16297(¶39); Appx10328-10329(328:25-329:5); Appx11585-11586(1585:20-1586:10).

Particle size (claims 19-21). Claims 19-21 recite "an average particle size (d50) of from about 1600 nm to about 900 nm." The court recognized that particle size is a result-effective variable. Appx83-84. The '544 patent's Formulation B discloses d(50) in the claimed range (1380nm). *See* Appx13242:

	Particle size (μm)			
Formulation	10%	50%	90%	specific surface area (m^2/g)
A	2.51	6.03	7.64	1.3
B	0.62	1.38	6.83	6.5
C	0.52	0.74	1.15	13.5
D	0.43	0.52	0.65	>15

The court concluded, however, that the '544 patent *taught away* from explicitly-disclosed Formulation B, because the '544 patent *also* taught formulations with d(90) less than 2000 nm, and Formulation B's d(90) measurement was 6830 nm. Appx84-85 (citing Appx13239(3:42-44), Appx13240(5:26-21), Appx13241(9:25-31), and Appx13242(10:27-29),

which are all passages from the written description, and calling those disclosures "effective particle size limitations").

c. The Court Found No Reasonable Expectation of Success

The court concluded that a POSA would have had no reasonable expectation of success because "developing a *generalized* multi-dose regimen using an LAI to initiate therapy was an unpredictable process." Appx87. In the court's view, "a POSA would need safety, efficacy, and pharmacokinetic data in order to evaluate how a *generalized* dosing regimen would perform in patients," but the prior art "contained no such data." Appx88.[4]

d. The Court Found "Secondary Considerations" Favored Janssen

Finally, the district court found that all of Janssen's secondary-considerations evidence favored nonobviousness. The court did not find that evidence "strong" or specify whether it did any work in the obviousness

[4] The Kramer reference did disclsoe *clinical data* showing "significant improvements" after day 8 for a regimen of 50 and 100 mg-eq. paliperidone palmitate injections on days 1, 8, and 36. Appx18047-18048 (abs.322). The court assumed Kramer was prior art, yet dismissed it, saying the "obviousness analysis *would be unaltered* because, unlike the '906 Patent, Kramer discloses unequal doses injected into the gluteal muscle only." Appx92-93 n.35.

analysis. Instead, the court simply rejected Teva's objections, and credited Janssen with having provided some evidence in various categories of "secondary considerations." Appx95-112. These included "industry praise" based on a *nomination* for an award Janssen did not win and may have nominated itself for, Appx100-101, "long-felt need" and "commercial success" based on Invega Sustenna sales, after denying that Janssen's numerous paliperidone patents dating to 1992 had any competition-blocking effect, Appx104-112, and accepting Janssen's own mistakes in development (*e.g.*, using the wrong needle length for buttock injections in an unclaimed regimen) as evidence of "unexpected results." Appx94-97.

2. Indefiniteness of the "Average Particle Size" Limitation (Claims 19-21)

Claims 19-21 recite "156 mg/ml of the paliperidone palmitate having *an average particle size* (d50) of from about 1600 nm to about 900 nm." Teva contended that limitation was indefinite for the same reasons the "molecular weight of 5 to 9 kilodaltons" was indefinite in *Teva v. Sandoz*: the claims recite a quantity that can be measured different ways with meaningfully different results, and the intrinsic evidence does not inform a POSA which to use.

Teva presented evidence that different measurement devices and techniques measure *different properties* of irregularly-shaped drug particles, model the particles as spheres, and estimate different things all called "average particle size," and that the results meaningfully differ. *See, e.g.*, Appx16306; Appx16318 (at least seven different properties); Appx20632-20633 (different sizes for Coulter and Mastersizer); Appx13179-13180 (different specifications based on which device used); *compare* Appx16498 (Teva reporting Lot FIB3801 using Masterizer as 700 nm), *with* Appx16413 (Janssen reporting Lot FIB3801 using Masterizer as 1100 nm); Appx10608-10609(608:24-609:2); Appx10609(8-14); Appx10609-10610(609:19-610:19). The court dismissed that evidence as inconsequential, or the result of a defective device, and upheld Janssen's claims. Appx132 & n.52.

3. Final Judgment

The district court entered final judgment against Teva, enjoining Teva and delaying approval of Teva's ANDA until after the '906 patent's expiration in 2031. Appx51-52(¶¶3-4). Because Mylan and Janssen had stipulated to be bound by the result of the Teva action, Appx49(¶2), the

court entered a similar final judgment in the Mylan action. Appx49-50. Teva and Mylan now appeal.

SUMMARY OF ARGUMENT

The judgments should be reversed, or, at a minimum, vacated and remanded.

I.A. The district court erred by requiring Teva to prove obviousness of unclaimed elements. "[N]either the particular motivation nor the avowed purpose of the patentee controls. *What matters is the objective reach of the claim*." *KSR*, 550 U.S. at 419-20. Yet, the district court's obviousness analysis repeatedly looks to potential motivations rather than the objective reach of the claims. The court repeatedly calls the claims "generalized," analyzing obviousness as if they recite dosing regimens that are *safe* and *rapidly effective* for *a majority of patients*, and criticizes Teva's evidence for failing to show that *such* regimens were obvious. Those may have been Janssen's goals, but they are not in the claims. The claims recite only administering a dosing regimen to "a" patient. For the renal-impairment claims, the court committed the same error by limiting the claims to patients with "mild" renal impairment and

criticizing Teva's evidence for failing to show the obviousness of that additional unwritten limitation.

I.B. The district court also erred by limiting the prior art only to *express* statements, while disregarding "the inferences and creative steps that a person of ordinary skill in the art would employ," *KSR*, 550 U.S. at 418. On the record at trial, each of the four distinctions the district court identified between claims and prior art (shoulder injections, unequal loading doses, dose-reduction for renally-impaired patients, and particle size) was well within the "predictable variations" a POSA would create. Shoulder injections are one of three standard intramuscular injection sites, and not anything Janssen discovered. The claimed loading doses are within prior art ranges and not shown to be special or critical. Dose-reduction for renally-impaired patients is a longstanding practice for drugs cleared through the kidneys. Particle size is a result-effective variable, which the prior art taught how to adjust and how it affects results. These were all distinctions without an inventive difference.

I.C. The district court did not state that secondary considerations independently supported the judgment or were even "strong"; only that those considerations weighed in Janssen's favor. That portion of the

opinion is thus no impediment to reversal or vacatur of the obviousness judgment, and this Court need not reach it. To the extent the Court reaches secondary considerations, the district court's opinion only contains additional errors. Janssen's "unexpected results" and "industry praise" evidence fall far short of what precedent requires. The purported "copying" concerns a property that affects *bioequivalence* and is thus not evidence of nonobviousness in this Hatch-Waxman case. And the "commercial success" and "long-felt" need ignore powerful evidence of blocking patents that prohibited competition for *fourteen years* before the critical date. No "secondary considerations" can support the judgment.

II. The district court separately erred by finding Janssen's claimed particle size range in claims 19-21 sufficiently definite. Undisputed evidence demonstrated that different particle-size-measurement devices and techniques measure different properties and produce meaningfully different results for paliperidone palmitate. The '906 Patent's written description and prosecution history provide no guidance regarding *which measurement method to use*. And because that choice impacts whether a given sample infringes the claimed range, the claims are indefinite. *Teva v. Sandoz*, 789 F.3d at 1344-45; *Dow*, 803 F.3d at 634.

ARGUMENT

Standard of Review

Following a bench trial, legal conclusions are reviewed *de novo*, and factual findings are reviewed for clear error. *Inwood Laby's, Inc. v. Ives Lab'ys, Inc.*, 456 U.S. 844, 855 (1982). Obviousness is a legal question, based on underlying facts. *Eisai Co. v. Dr. Reddy's Lab'ys, Ltd.*, 533 F.3d 1353, 1356 (Fed. Cir. 2008). Claim construction and indefiniteness are questions of law reviewed *de novo*, with any underlying fact findings reviewed for clear error. *Teva Pharms. USA, Inc. v. Sandoz, Inc.*, 574 U.S. 318, 325-26, 331 (2015); *Teva v. Sandoz*, 789 F.3d at 1341.

I. The Non-Obviousness Judgment Should be Reversed or Vacated as to All Claims.

To demonstrate obviousness, a patent challenger must generally show that a POSA "would have had reason to combine the *teaching* of the prior art references to achieve *the claimed invention*, and … would have had a reasonable expectation of success." *In re Cyclobenzaprine*, 676 F.3d 1063, 1069 (Fed. Cir. 2012).

Under the proper analysis, obviousness should not have been a difficult question. All Janssen did was select one regimen from ranges and

parameters disclosed in prior-art paliperidone palmitate patents and applications, without showing that its selected regimen produced different results. Prior art disclosed LAI formulations of paliperidone palmitate, clinical uses, aqueous nanoparticle formulations, durational efficacy, *the exact Invega Sustenna formulation*, and *the same* loading and maintenance doses that the '906 patent claims. As shown below for claim 2, the '548 protocol and WO'384 already taught the claimed doses.

Claim 2		
Claimed Dose/Timing	**Claimed Dose Amt./Site**	**Prior Art Dose Disclosure**
Loading dose, Day 1	150 mg-eq. shoulder	**'548 protocol** taught loading doses of 50, 100, or 150 mg-eq. / buttock
Loading dose, Day 6-10	100 mg-eq. shoulder	**'548 protocol** taught loading doses 50, 100, or 150 mg-eq. / buttock
Maintenance dose, "1 month (±7 days) after" second loading dose	25-150 mg-eq. shoulder or buttock	**WO'384** taught 25-150 mg-eq. injections
Maintenance doses, "monthly (±7 days) intervals"	25-150 mg-eq. shoulder or buttock	**WO'384** taught 25-150 mg-eq. injections

"[T]ak[ing] account of the inferences and creative steps that a person of ordinary skill in the art would employ," *KSR*, 550 U.S. at 418, the differences between the claims and prior art are insubstantial: selecting

from among three known injection sites, varying the loading doses among three options explicitly taught in the prior art and within a prior-art range, and—for subsets of claims—following prior-art teachings to give renally-impaired patients lower doses and to size particles according to the '544 patent. The district court should have ruled the '906 patent obvious.

The court reached the opposite result and extended Janssen's ongoing 20-year paliperidone palmitate monopoly to 2031 by committing two fundamental errors.

First, the district court erroneously required Teva to prove the obviousness of *unclaimed* elements. The court criticized Teva's evidence for failing to show obviousness of "*generalized*" dosing regimens that are *safe* and *rapidly effective* for *a majority of patients*. *E.g.*, *supra* pp. 25-29; Appx78 ("[t]he '906 patent, however, claims a generalized dosing regimen"); Appx79 (distinguishing prior-art as "teach[ing] individualized, rather than generalized, dosing"); Appx87 (similar); Appx88 (similar); Appx72 (requiring safety and efficacy data from prior art); Appx74 (similar); Appx73-74 n.26 (similar); Appx88 (similar). But the claims recite only administering a dosing regimen to "a" patient, nothing more. For

the renal-impairment claims, the court similarly criticized Teva's evidence for failing to show obviousness of an unwritten "mild" renal-impairment limitation.

Second, the district court limited the prior art to its precise, express disclosures, instead of considering what a person of skill in the art would understand or take away from it. Each of the four purported distinctions the court identified between the claims and prior art is only significant if one limits the prior art to express statements, rather than their overall teachings. Binding precedent rejects that mode of analysis.

A. The District Court Erred By Requiring Teva to Prove Obviousness of Unclaimed Elements.

Obviousness compares *the claims* with prior art. The question is whether "the differences between *the subject matter sought to be patented* and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art…." 35 U.S.C. §103 (2006).[5] Supreme Court precedent reiterates that basic but critical point. *KSR*, 550 U.S. at 419-20 ("What matters is the *objective reach of the claim*. If the claim extends to

[5] The '906 patent is based on an application filed in 2008.

what is obvious, it is invalid under §103."); *Graham v. John Deere Co.*, 383 U.S. 1, 17 (1950) ("differences between the prior art *and the claims* at issue are to be ascertained").

This Court's precedent is to the same effect. It is a "long-established rule that claims which are broad enough to read on obvious subject matter are unpatentable even though they also read on non-obvious subject matter." *Muniauction v. Thomson Corp.*, 532 F.3d 1318, 1328 n.4 (Fed. Cir. 2008). And it is legal error to require a patent challenger to prove obviousness of unclaimed limitations. *E.g.*, *Canfield*, 987 F.3d at 1383 (reversing nonobviousness ruling where PTAB relied on unclaimed limitations); *Senju Pharm. Co. v. Lupin Ltd.*, 780 F.3d 1337, 1347 (Fed. Cir. 2015) (upholding obviousness judgment; prior art failure to disclose "corneal permeability" is "not relevant to the obviousness determination" because it "is not a limitation" of the claims); *Allergan v. Apotex*, 754 F.3d at 962-63 (where claims covered a class of compounds, district court erred by focusing on obviousness of a single compound within the class); *Allergan, Inc. v. Sandoz Inc.*, 726 F.3d 1286, 1292 (Fed. Cir. 2013) (same); *MobileMedia Ideas, LLC v. Apple Inc.*, 780 F.3d 1159, 1172 (Fed. Cir.

2015) (reversing nonobviousness judgment where patentee's expert "provided only testimony unrelated to the actual [claim] limitations").

The district court committed that error multiple times—for all claims by requiring Teva to prove the obviousness of "generalized" dosing regimens, and again for the renal-impairment claims by requiring proof of the obviousness of reduced doses for patients with "mild" renal impairment. Here, as in cases like *Canfield* and *Allergan v. Apotex*, the judgment must be reversed.

1. For All Claims, the District Court Erroneously Required Teva to Prove Obviousness of "Generalized" Dosing Regimens That Would be Safe and Effective for a Majority of Patients.

If Janssen wanted to claim a broadly applicable method for treating schizophrenia in a generalized patient population, it could have done so. It did not. Every asserted claim recites "A dosing regimen for administering paliperidone palmitate to *a psychiatric patient in need of treatment*" (or "a renally impaired psychiatric patient in need of treatment"), by administering specified doses. The claims include no further limitations requiring therapeutic effect (rapidly or otherwise) or avoidance of

side effects, let alone requiring such results for any broader patient population. The question for obviousness purposes is whether it would be obvious to administer the *claimed* dosing regimen.

Under the proper analysis, the claims are obvious. The '544 patent claimed a method of treating schizophrenia with monthly intramuscular injections for paliperidone palmitate. The '548 protocol already taught that loading doses of 150, 100, or 50 mg-eq. on days 1 and 8 were "thought to be safe and effective" and the study was merely to "confirm[]" as much "in the larger patient population." Appx10316-10317(316:17-317:2); *see* Appx13244-13245; Appx10207(5-23); Appx10758(6-25); Appx11124(11-20); Appx11135(5-11). And WO'384 taught monthly maintenance doses of 25-150 mg-eq., "depending on the dose needed," using the exact Invega Sustenna formulation. *Compare* Appx13316-13317(tbls.6, 7), *with* Appx166(tbls.2, 3); *see also* Appx13308(9:9-11); Appx13316(tbl.6); Appx13317(18:10-15); Appx10303-10304(303:22-304:7); Appx10305(9-21); Appx12163(8-20).

The district court reached a different answer because it asked a different question. Instead of comparing prior art to the *claims*, the court asked whether it would be obvious to a skilled artisan that the claimed

regimens would be *safe* and *rapidly effective* for a "*generalized*" patient population. *E.g.*, Appx78; Appx79 The court's obviousness analysis relied on that distinction between "generalized" and "individualized" dosing regimens at every step, grafting FDA regulatory requirements onto the claims.

After declaring that "[t]he '906 Patent … claims a *generalized* dosing regimen," Appx78, the court relied on the "generalized"/"individualized" distinction to distinguish prior art. Appx79 (prior art "teach[es] *individualized*, rather than *generalized*, dosing"). In that vein, the court criticized the prior art for lacking clinical data the court believed necessary to make a "generalized" dosing regimen obvious. Appx88 ("a POSA would need safety, efficacy, and pharmacokinetic data in order to evaluate how a *generalized* dosing regimen would perform in patients."); *see also* Appx71-74 (criticizing prior art for lacking "clinical results or safety data," or evidence of "rapid and sustained efficacy"); Appx91 n.34 (same); Appx92 (same). And the court relied on the same "generalized"/"individualized" distinction to find no motivation to combine or modify prior art, and no reasonable expectation of success. Appx78 (distinguishing prior

art because it "would suggest [modifications on] an *individualized* basis."); Appx87 ("the record establishes that developing a *generalized* multi-dose regimen using an LAI to initiate therapy was an unpredictable process"). Under that reasoning, no dosing regimen would be obvious until tested on a wide swath of the patient population.

Under binding precedent that was legal error. Just as the PTAB erred in *Canfield* by upholding claims based on the prior art's failure to disclose unclaimed "placement" limitations, the district court erred in *Allergan v. Apotex* by focusing on a compound within a claimed class, and the appellant erred in *Senju* by relying on an unclaimed "corneal permeability" property, the district court erred here by upholding the claims based on unclaimed requirements of "generalized" safety and rapid efficacy. *Canfield*, 987 F.3d at 1383; *Senju*, 780 F.3d at 1347; *Allergan v. Apotex*, 754 F.3d at 962-63.

And to be clear, there is no support in the '906 patent's specification for the district court's reading. Quite the opposite. Like the claims, the written description uses the same "*a* psychiatric patient" language to describe "the invention." Appx159-160(2:11-4:39) ("a dosing regimen for administering paliperidone palmitate to *a* psychiatric patient in need of

treatment"). And it refers repeatedly to adjusting doses for individual patients—as opposed to expecting any single regimen to be broadly effective. *See, e.g.*, Appx165(14:13-26) ("[t]hose of skill in the treatment of diseases *could easily determine the effective amount of paliperidone to administer*" based on a patient's body weight); Appx161(5:31-34) ("*[A]t least* a first loading dose of 150 mg-eq…should be administered"); Appx161(5:34-38) ("*Preferably* the first two doses will be loading doses of between *from about 100 mg-eq. to about 150 mg-eq*."); Appx170(23:16-24) (noting 150/100, 100/100 and 150 mg-eq. alone all work as loading doses); *see also* Appx170(23:26-24:26); Appx174(31:30-49). Not once does the patent refer to any dosing regimen as "generalized." Whether viewed as an erroneous implicit claim construction or an erroneous application of the obviousness test, the district court erred in treating the claims in this manner.

If more is needed, reliance on the "generalized"/"individualized" distinction led the district court into further error when it required *clinical data* from the prior art. *See, e.g.*, Appx88 ("a POSA would need safety, efficacy, and pharmacokinetic data in order to evaluate how a *generalized* dosing regimen would perform in patients."); Appx71-74 (criticizing prior

art purported lack of "clinical results or safety data" or evidence of "rapid and sustained efficacy"). This Court has rejected precisely such "a rigid rule categorically precluding obviousness determinations without pk/pd data." *Yeda Research v. Mylan Pharms. Inc.*, 906 F.3d 1031, 1043 (Fed. Cir. 2018). *Yeda* considered claims that *required* efficacy, and affirmed that *even those* claims were obvious in light of prior art that simply taught "a therapeutically effective formulation to a POSITA." *Id.* at 1044. *Yeda* reasoned that "pk/pd data was largely irrelevant" because there were "a wide range of likely efficacious doses." *Id.* In other words, prior-art disclosures of effective doses was enough; granular data *confirming* the claimed efficacy was not required. Janssen's claims do not require efficacy at all. The district court thus erred by faulting prior art for supposedly lacking clinical efficacy data. Here, as in other cases upholding claims based on purported nonobviousness of unclaimed elements, the judgment must be reversed. *Canfield*, 987 F.3d at 1383; *Allergan v. Apotex*, 754 F.3d at 962-63; *Allergan v. Sandoz*, 726 F.3d at 1292.

2. For the Renal-Impairment Claims (8, 11, and Dependents), the District Court Further Erred by Requiring Proof of Obviousness of an Unwritten "Mild" Renal-Impairment Limitation.

The renal-impairment claims (8, 11 and dependents) all include the same "*a* psychiatric patient" language and are equally affected by the error of requiring proof that "generalized" dosing regimens were obvious. The district court further erred with respect to those claims by requiring proof of obviousness of an unwritten "mild" limitation. Claims 8, 11, and dependents recite "dosing regimen[s] for administering paliperidone palmitate to a *renally impaired* psychiatric patient." No claim limits the term "renally impaired." POSAs undisputedly recognize "mild," "moderate," and "severe" levels of renal impairment, Appx10116(4-5), meaning "renally impaired" encompasses all three. It was thus sufficient to prove the obviousness of those claims with prior-art references teaching dosing for *any level of renal impairment*, or that did not specify a degree of impairment. *Muniauction*, 532 F.3d at 1328 n.4.

The district court, however, upheld the renal-impairment claims by limiting them to "mild" renal impairment. Quoting Janssen's brief without elaboration, the court declared "the '906 Patent 'focuses on *mild* renal

impairment.' Pls. Br. at 70," Appx82 (quoting Appx1219), and distinguished prior art on that basis. Appx82 ("In contrast, the '906 Patent 'focuses on mild renal impairment.'"); Appx82-83 ("the dosing regimens address patients with mild renal impairment, and neither the '591 Application nor Cleton 2007 [Appx14112] expressly teach LAI paliperidone palmitate dose reduction for mild renal impairment."); Appx83 (finding prior art "would not motivate a POSA to arrive at the claimed dosing regimens for patients with mild renal impairment.").

Just as it was error to require proof of obviousness of unwritten "generalized" dosing-regimen limitations, it was further error to require proof of obviousness of an unwritten "mild" renal-impairment limitation. There is no support in the specification for any such limitation. Embodiments and examples do not limit patent claims. *Phillips v. AWH Corp.*, 415 F.3d 1303, 1323 (Fed. Cir. 2005) (en banc). Only unambiguous statements of lexicography or disclaimer do. *Thorner v. Sony Comput. Entm't Am. LLC*, 669 F.3d 1362, 1365 (Fed. Cir. 2012); *Hill-Rom Servs., Inc. v. Stryker Corp.*, 755 F.3d 1367, 1371 (Fed. Cir. 2014). Nothing in the '906 patent defines "renally impaired" to mean "mildly renally impaired" or disclaims moderate or severe renal impairment. The written description

states that "[f]or patients with *mild* renal impairment the loading doses should be reduced to 75 mg-eq. for the first two loading doses." Appx161(5:56-61). That merely states how patients with mild renal impairment should be treated; it does not define "renally impaired."

As with the full set of claims, the judgment upholding the renal-impairment claims rests on the legal error of requiring proof of obviousness of unclaimed limitations.

B. The District Court Erred by Considering Prior Art Only for What it Expressly States Rather Than What it Fully Teaches, and by Disregarding the Perspective of a Skilled Artisan.

The district court compounded its errors by giving the prior art a stingy read. In *KSR*, the Supreme Court rejected a "rigid approach" to obviousness that unduly limits the prior art and the skill of a POSA. 550 U.S. at 415. The Court reversed a nonobviousness judgment, and explained that the proper analysis is "expansive and flexible," and not "confined by…overemphasis on the importance of published articles and the explicit content of issued patents." *Id* at 415, 419. Courts must "take account of the inferences and creative steps that a person of ordinary skill in the art would employ," recognizing that "[a] person of ordinary skill is also a person of ordinary creativity, not an automaton." *Id.* at 418, 421.

Consistent with *KSR*, this Court's precedent instructs that prior art "must be considered *not only for what it expressly teaches*, but also for what it fairly suggests" to a skilled artisan. *Bradium Techs. LLC v. Iancu*, 923 F.3d 1032, 1049 (Fed. Cir. 2019) (affirming obviousness, quoting *In re Baird*, 16 F.3d 380, 383 (Fed. Cir. 1994)); *see Belden v. Berk-Tek LLC*, 805 F.3d 1064, 1076 (Fed. Cir. 2015) (similar); *In re Mouttet*, 686 F.3d 1322, 1331 (Fed. Cir. 2012). The "normal desire of scientists or artisans to improve upon what is generally known" is generally sufficient to overcome minor differences between claims and prior art. *In re Peterson*, 315 F.3d 1325, 1330 (Fed. Cir. 2003); *see also E.I. DuPont de Nemours & Co. v. Synvina C.V.*, 904 F.3d 996, 1011 (Fed. Cir. 2018) (quoting *Peterson*, reversing nonobviousness judgment); *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1368 (Fed. Cir. 2007) (same).

Indeed, for recurring scenarios, this Court's precedent provides additional guideposts. Where prior art discloses a range that overlaps with a claimed range or points, the claims are presumptively obvious unless there is evidence that the claimed range or points are special or critical. *Almirall, LLC v. Amneal Pharms., LLC*, 28 F.4th 265, 272 (Fed. Cir. 2022). And when a variable is known to be "result-effective," "it is not

inventive to discover the optimum or workable ranges by routine experimentation." *In re Applied Materials, Inc.*, 692 F.3d 1289, 1295 (Fed. Cir. 2012).

The district court's obviousness analysis upholds Janssen's claims by doing exactly what precedent instructs not to do. All four distinctions the court identified between any claims and individual prior-art references—shoulder injections, unequal loading doses, reduced doses for renally-impaired patients, and particle size—were only "differences" in the first place because the district court improperly limited each prior-art reference to its explicit disclosure. The court allowed no role for "predictable variation" by a skilled artisan, *KSR*, 550 U.S. at 417, and reasoned in essence that the claims are not obvious because no individual reference anticipates. Under the correct standard, the claims are obvious.

1. Shoulder Injections Cannot Distinguish the Claims from Prior Art (All Claims).

Neither the court nor Janssen disputed that the shoulder is one of three common intramuscular injection sites, whose advantages and disadvantages are well known. *Statement of Case §D.1.* Janssen did not invent shoulder injections, nor discover any new property of shoulder in-

jections. Appx11719(15-17); Appx12311(6-21). Although prior art actually taught *shoulder* injections of paliperidone palmitate, Appx16206 (2006 study, "Paliperidone Palimitate Injected Into the Shoulder or the Buttock…."); Appx16204 (similar), there was no need for an express prior-art disclosure of shoulder injections. Prior-art disclosures of intramuscular injections—regardless of location—should have been sufficient. The '544 patent's claims recite intramuscular paliperidone palmitate injections, Appx13242, and are presumed enabled. *In re Antor Media Corp.*, 689 F.3d 1282, 1288 (Fed. Cir. 2012).

Shoulder injections were undisputedly one of "a finite number of identified, predictable solutions" within the "technical grasp" of a skilled artisan. *KSR*, 550 U.S. at 421; *Yeda*, 906 F.3d at 1043-44 (dosing-regimen claims were obvious where prior art disclosed "a finite and known pool of dose and frequency options"); *Almirall*, 28 F.4th at 273 (obvious claims were "simply a case of substituting one known gelling agent for another," where tradeoffs were "just a property of the particular known material, subject to conventional experimentation."). The district court therefore erred when it placed significance on the shoulder injection site.

The reasoning distinguishing primary prior-art references for not expressly reciting shoulder injections, Appx74-75; Appx69 n.20, and discounting reference books for not disclosing "deltoid administration of LAI loading doses," Appx76, cannot support the judgment.

2. Unequal Loading Doses Cannot Distinguish the Claims from Prior Art (All but Renal-Impairment Claims).

All claimed loading doses (150mg-eq. and 100mg-eq.) are within prior art ranges and explicitly disclosed in prior art. As noted, WO'384 describes a range of 25-150 mg-eq. doses, and the '548 protocol discloses 50, 100, or 150 mg-eq. loading doses on days 1 and 8. *Statement of Case §C.2-3, supra.* Under the proper analysis, the "unequal loading doses" should have been presumed obvious, as Janssen presented no evidence they were special or critical. *Almirall*, 28 F.4th at 272.

Evidence confirmed, moreover, that a skilled artisan would implement "predictable variation[s]," *KSR*, 550 U.S. at 417, such as reducing doses for patients with smaller bodies or milder symptoms (*e.g.*, 150/100, 100/100, or 100/50 mg-eq. on days 1 and 8) to avoid overexposure. Appx10148(17-19); Appx10321-10323(321:1-323:1); Appx10474-10475(474:20-475:22). The 1990s Ereshefsky articles described loading

doses of LAI antipsychotics. *Statement of Case §D.1, supra*; Appx14113-14120; Appx14121-14129. The '906 patent acknowledges that "[t]hose of skill in the treatment of diseases could easily determine the effective amount of paliperidone to administer" for specific patients and diseases. Appx165(14:13-26). Janssen's expert likewise admitted that "knowing that paliperidone palmitate could be administered as a long-acting injectable once monthly," a POSA would "be motivated to try loading dose regimens" "if their goal was to speed onset." Appx11792-11793(1792:16-1793:5). In these circumstances, it was no answer for the district court to discount the Ereshefsky articles because they concerned a different drug, or to discount the '548 protocol because it taught equal loading doses. Appx78-79. All Janssen did was to take known elements from prior art and arrange them in an obvious way.

3. Dose-Reduction for Renally-Impaired Patients Cannot Distinguish the Claims from Prior Art (Claims 8, 11, and Dependents).

Reduced doses of paliperidone for renally-impaired patients were not novel. It was known by 2007 that paliperidone is cleared mainly through the kidneys, exposure to paliperidone "basically doubl[es]" for patients with impaired renal function, and that paliperidone doses

should be reduced for renally-impaired patients. *Statement of Case §D.3, supra*. Indeed, the prior art Invega ER label (oral paliperidone) advises to cut the maximum allowable dose in half for renally-impaired patients, Appx16233; Appx10098(10-17); Appx17941-17942. It is obvious—indeed, standard procedure—to reduce doses by approximately half for renally-impaired patients.

Moreover, all doses recited in claims 8 and 11 (75mg-eq. loading doses, and 25-75 or 25-50 mg-eq. maintenance doses) for renally-impaired patients are *within prior-art ranges*, and are approximately half of specific high doses disclosed in the prior art. The district court thus should have recognized that Janssen's renal-impairment claims were predictable variations on prior art. A skilled artisan treating a *single patient* with renal impairment would have known how to vary doses for patients with normal renal function, and would have started by cutting any dose approximately in half. Appx10332-10333(332:21-333:20); *see* Appx10150(8-14); Appx10529(23-25); Appx10474-10475(474:20-475:22).

The district court's contrary reasoning is unsupportable. *First*, the court concluded the renal-dosing claims are nonobvious because the

claimed loading doses (two 75 mg-eq. doses) are not *precisely* half of loading doses in *other claims* (150mg-eq. and 100 mg-eq. loading doses). Appx83. That was not Teva's argument, and the proper comparison is to prior art, not other claims. As Teva contended, but the court apparently missed, the loading doses in claims 8 and 11 are exactly half of the high loading doses *in the '548 protocol*, and well within the disclosed range. Appx10332-10333(332:21-333:20).

Second, the court discounted prior-art disclosures regarding oral paliperidone because they did not expressly concern paliperidone palmitate. Appx81-83. The trial evidence was unequivocal, however, that "renal function is the driver. Dosage form is not as important." Appx10531(15-20). It was known and undisputed that the body converts injected paliperidone palmitate to active paliperidone, which it then clears in the exact same way as oral medication. Appx10102-10103(102:24-103:23); Appx10148(1-12); *see* Appx10532(18-21) ("the mechanism of clearance is the same."). The Invega Sustenna label acknowledges the direct correlation between paliperidone palmitate and oral paliperidone. Appx13120. Only by limiting the prior art artificially

to express statements, and disregarding the perspective of a skilled artisan can the renal-impairment claims be distinguished from prior art.

4. Particle Size is a Result-Effective Variable That Prior Art Taught How to Optimize, and Thus Cannot Distinguish the Claims from Prior Art (Claims 19-21).

When a variable is known to be "result-effective," "it is not inventive to discover the optimum or workable ranges by routine experimentation." *Applied Materials*, 692 F.3d at 1295 (Fed. Cir. 2012); *In re Boesch*, 617 F.2d 272, 276 (CCPA 1980) ("[D]iscovery of an optimum value of a result effective variable in a known process is ordinarily within the skill of the art."). "A recognition in the prior art that a property is affected by [a] variable is sufficient to find the variable result-effective." *DuPont*, 904 F.3d at 1009.

The '544 patent and WO'384 disclosed not only that paliperidone palmitate particle size is a result-effective variable, but also *how* particle size affects results and *how* to adjust particle size. The '906 patent described the '544 patent as providing "[s]uitable aqueous nano particle depot formulations." Appx162(7:42-44). The '544 patent, in turn, explained that paliperidone palmitate's pharmacokinetics "depend on the particle size to a much larger extent than previously held possible."

Appx13239(3:46-55); *Statement of Case §C.1, supra*. The '544 patent and WO'384 further disclose a preferred range of particle sizes (d(90) less than 2000 nm) that encompasses the '906 patent's claims, and a milling process to control particle size. Appx13239(3:65-4:3); Appx13304(5:23-25); Appx13306(7:25-26); Appx13240(6:10-17); *see also* Appx10294-10295 (294:20-295:25); Appx11779-11780(1779:22-1780:1); Appx11781(17-19).

Under this Court's precedent, the claimed particle sizes are obvious as a matter of law. Particle size is a result-effective variable, and Janssen's purported discovery of a workable range of sizes is not patentable. *DuPont*, 904 F.3d at 1011. The district court held otherwise only by confining the '544 patent's disclosure to the four specific examples on the page. Appx84; Appx13241(8:44-57). Worse, because one example (Formulation B) with a particle size within the claimed d(50) range had a d(90) parameter outside the '544 patent's preferred range, the court concluded that "the '544 Patent *expressly teaches away* from using this formulation." Appx84-85. That is not "teaching away." As this Court has repeatedly held, "[a] teaching that a composition may be optimal or standard does not criticize, discredit, or otherwise discourage investigation into other compositions." *Galderma Labs., L.P. v. Tolmar, Inc.*, 737

F.3d 731, 738-39 (Fed. Cir. 2013). A reference that teaches a preferred range and an example outside that range teaches two things; it does not "teach away" from one or the other.

C. Secondary Considerations Cannot Support the Judgment or Prevent Reversal or Vacatur.

Obviousness compares the claims to what the prior art teaches a skilled artisan. The district court legally erred on both sides of the comparison. It required Teva to prove obviousness of unclaimed limitations (§I.A, *supra*), and it limited the prior art to its express statements (§I.B, *supra*). For either reason or both, the nonobviousness judgment must be reversed or vacated, and this Court need go no further.

Although the district court found that secondary considerations weighed in Janssen's favor, it did not state that the evidence was "strong" or *independently* sufficient to support the nonobviousness judgment—nor could it. Secondary considerations "without invention will not make patentability," *Sakraida v. Ag Pro, Inc.*, 425 U.S. 273, 283 (1976) (quoting *Great Atl. & Pac. Tea Co. v. Supermarket Equip. Corp.*, 340 U.S. 147, 153 (1950)), and they are no impediment to reversal or remand here. *E.g., Ohio Willow Wood Co. v. Alps S., LLC*, 735 F.3d 1333, 1344 (Fed. Cir. 2013) (affirming summary judgment of obviousness despite secondary-

considerations evidence); *Wyers v. Master Lock Co.*, 616 F.3d 1231, 1244-46 (Fed. Cir. 2010) (reversing nonobviousness judgment, despite jury verdict and secondary-considerations evidence).

To the extent secondary-considerations evidence played any meaningful role in the judgment, that was further error. Such evidence is only relevant to the extent it "give[s] light to the circumstances surrounding the origin of *the subject matter sought to be patented*." *Graham*, 383 U.S. at 17-18. Thus a "nexus is required between the merits of the claimed invention and the evidence offered." *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1539 (Fed. Cir. 1983). For specific secondary considerations, precedent establishes further guideposts. The district court, however, uncritically accepted Janssen's arguments and "appears to have fallen into the understandable but improper trap of constructing a selective version of the facts relating to the objective considerations so as to confirm its hunch" that the asserted claims were not obvious. *In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Pat. Litig.*, 676 F.3d 1063, 1080 (Fed. Cir. 2012).

1. There is No Evidence of "Unexpected Results"

The district court found "unexpected results" because it found **(1)** conventional wisdom regarding dosing was to "start low and go slow"; and **(2)** Janssen unexpectedly (to Janssen) failed, then unexpectedly (to Janssen) succeeded, in its own development process. Appx94-97; *see also* Appx89 (referencing "lower initial doses followed by slow upward adjustments" in context of reasonable expectation of success). "Unexpected results" may be relevant if unexpected from a POSA's (not a party's) perspective, unexpected compared to the closest prior art, and if they differ in kind rather than degree from prior art. *Kao Corp. v. Unilever U.S., Inc.*, 441 F.3d 963, 970 (Fed. Cir. 2006); *Galderma,* 737 F.3d at 739.

Janssen's evidence is none of those things. The trial evidence showed higher loading doses led more quickly to higher blood concentrations of paliperidone, which is what a POSA would have expected. *E.g.*, Appx11793(2-5) ("speeding onset of efficacy for an antipsychotic drug would be a known important goal"); Appx12118-12119(2118:8-2119:2) (POSA would expect correlation between dose amount and blood concentration over time).

a. The District Court Erred In Finding a Difference in Kind

"Unexpected results that are probative of nonobviousness are those that are *different in kind and not merely in degree* from the results of the prior art." *Galderma*, 737 F.3d at 739. "Results which differ by percentages are differences in degree … where the modification of the percentage is within the capabilities of one skilled in the art at the time." *Id.*; *see also In re Budde*, 319 F.2d 242, 246 (CCPA 1963) (ranges of reaction time and temperature were difference in degree); *In re Harris*, 409 F.3d at 1339, 1344 (Fed. Cir. 2005) (32-43% increase in stress rupture "does not represent 'difference in kind'").

The district court found a difference in kind because "Invega Sustenna improved patient treatment adherence through its use of high initial loading doses that rapidly achieved therapeutic concentrations of paliperidone palmitate and monthly loading doses which maintained these concentrations." Appx96-97. But Janssen admitted that *numerous* unclaimed dosing regimens achieved that same goal. Appx170(23:16-24); *see also* Appx170(23:26-24:26); Appx174(31:30-49). And Janssen's own modeling of data from other trials shows that the only difference between

dosing regimens is the percentage of *total* patients that would expect to achieve efficacy by a certain day:

Dosing Regimen	**% of Patients Expected Efficacy by Day 8**	
	Shoulder	**Buttock**
25/100 mg-eq., Days 1 and 8	20%	8%
50/100 mg-eq., Days 1 and 8	49%	26%
100/100 mg-eq., Days 1 and 8	73%	52% *('548 protocol)*
150/100 mg-eq., Days 1 and 8	84% *(claimed)*	66%

Appx41907. And to be clear, the "results" are *predictions* generated by computer models, not actual experiments. Regardless, such differences in degree are insufficient as a matter of law to support non-obviousness. *Galderma*, 737 F.3d at 739; *In re Budde*, 319 F.2d at 246; *In re Aller*, 220 F.2d 454, 456-57 (CCPA 1955); *In re Harris*, 409 F.3d at 1344.

b. The District Court Failed to Compare the Claims to the Closest Prior Art.

Unexpected results "must be shown to be unexpected *compared with the closest prior art*." *Kao*, 441 F.3d at 970. No party argued that "start low and go slow" is the closest prior art. Indeed, the related '548 protocol taught dosing regimens as high as 150 mg-eq. on days 1 and 8, which is neither "low" nor "slow."

Although the district court also compared the claims to the '548 protocol, Appx96, it erroneously looked to *Janssen's own expectations* rather than a POSA's. Janssen offered no evidence of what POSA would have expected from the claimed regimen based on the '548 protocol. Appx11610(3-7) (Janssen expert Sinko addressed only "copying and failure of others"); Appx11907-11910(1907:7-1910:5); Appx11914-11915(1914:21-1915:13) (Janssen expert Kohler discussed only industry praise and purported "clinical benefits"). The only evidence of *any* expectation comes from Janssen's employees, whom the district court found "*expected*…success" from the '548 protocol. Appx96. Because "the record is devoid of *any* evidence of what the skilled artisan would have expected," the unexpected results finding is clear error. *Pfizer*, 480 F.3d at 1371 (original emphasis); *In re Geisler*, 116 F.3d 1465, 1470 (Fed. Cir. 1997). If more is needed, the claimed regimen was never shown to produce better, or even different, results from the '548 protocol.

c. The District Court Erroneously Treated *Janssen's Mistakes* as Evidence of Non-Obviousness.

Finally, the district court erred by basing a skilled artisan's "expectation" on Janssen's mistakes. The court emphasized that Janssen considered the '548 protocol a "failed study," but ignored the reasons for failure. The study undisputedly "failed" only because Janssen **(1)** administered the wrong regimens to some patients; and **(2)** used insufficiently long needles for buttock injections of higher-BMI patients.

First, although the Protocol called for one group to receive 150 mg-eq. doses, a "medication kit allocation error" by Janssen meant that *more than two-thirds* of subjects (71 of 101) did not receive all intended doses. Appx36411-36413(tbl.2); Appx36445; Appx10894(1-3, 6-17); Appx11063-11064(1063:24-1064:12); Appx11168-11169(1168:22-1169:25). As the district court noted, that error "had nothing to do with the 150-milligram dose regimen itself," Appx70 n.23 (quoting Appx10895(1-7), citing Appx1586-1587(¶560)), yet precluded Janssen from showing statistically significant improvement using the 150 mg-eq. regimen, Appx36640. And regardless, the court found that 100 mg-eq. "establish[ed] statistical efficacy," and thus *was successful*. Appx71; *see also* Appx36640 ("Both the

paliperidone palmitate 100 and 50 mg gq. groups showed statistical superiority compared to the placebo group…").

Second, Janssen used overly short needles for buttock injections. Janssen knew that buttock injections typically required a 2-inch needle to ensure *intramuscular* injection. Appx10900(13-16) (2-inch needle for Risperdal Consta); Appx20771 ("the mean gluteal-fat thickness (5.0 cm) exceeds the length of the needle (3.8 cm)."). Otherwise, the drug could be injected into fat and poorly perfused. Appx20771; *see also* Appx17972; Appx11156(2-17). Janssen nonetheless used a 1.5-inch needle for buttock injections, Appx10900(13-16); Appx26931, then claimed surprise when higher-BMI patients failed to show efficacy. Appx36463; Appx36639; Appx10795-10796(795:17-796:4); Appx11055(16-25) ("the drug was less effective, or not effective at all" in patients with high BMI); Appx11061(21-24) (same for '548 protocol). Subjects with average BMI were treated effectively as expected.

By the time of the '548 protocol study, however, it was too late to change the needle length because Janssen lacked *any* clinical data for 2-inch needles. To avoid the "nightmare" scenario of "starting the technical development all over again," Appx10902(3-5); Appx23028; *see also*

Appx11437(6-16), Janssen simply switched its loading doses to the shoulder because it already had predictive data. Appx10902(10-13) Appx10903(11-18); Appx11371(9-13); Appx11450(11-16); *see also* Appx41869. And the FDA approved the regimen with two loading-dose shoulder injections without requiring a new trial. Appx11131(1-12); Appx11389-11390(1389:17-1390:17).

It should be beyond dispute that Janssen idiosyncratically bungling its own experiments is not evidence of a POSA's expectations. *See Hoffmann-La Roche Inc. v. Apotex Inc.*, 748 F.3d 1326, 1330 (Fed. Cir. 2014) ("failure to generate statistically significant results points to a fault in the study," not nonobviousness). Instead of addressing the facts, the district court simply accepted Janssen's "failed study" label and argument that its results were "unexpected." Appx74; Appx96; Appx115.

2. The "Industry Praise" Finding Lacks Nexus and Record Support.

"Industry praise must … be linked to the patented invention." *Geo M. Martin Co. v. Alliance Machine Sys. Int'l LLC*, 618 F.3d 1294, 1305 (Fed. Cir. 2010). "[B]are journal citations and self-referential commendation" are not relevant. *Bayer Healthcare Pharms., Inc. v. Watson*

Pharms., Inc., 713 F.3d 1369, 1377 (Fed. Cir. 2013) (reversing nonobviousness judgment).

The district court dismissed data showing that use and prescribing practices use and prescribing practices, and instead cited Janssen's generic praise unconnected to the claims. Appx100. Three cited articles plainly lack nexus. One praises the benefits of LAIs generally, Appx20540; Appx20542, another states Invega Sustenna saves costs, Appx20567; Appx12323-12324(2323:17-2324:17), and the third states only that Invega Sustenna's regimen is "workable" and performed not "statistically significant[ly]" worse than haloperidol decanoate. Appx20552; Appx12412(9-23); Appx12443-12444(2443:8-2444:4). The remaining evidence is "self-referential commendation": articles *commissioned by Janssen* for sales purposes. Appx49986-49987; Appx12441(7-19); Appx12424-12425(2424:8-2425:5); and a *nomination* for an award that Janssen did not win, and for which Janssen may have nominated itself. Appx11046-11047(1046:12-1047:3); Appx11240-11241(1240:20-1241:3). Under this Court's precedent, none of this is evidence of nonobviousness of the actual claims of the '906 patent. *Bayer*, 713 F.3d 1377; *Geo. M. Martin*, 618 F.3d at 1305.

3. The District Court Misapplied the Law on Copying

In any patent case, "the mere fact of copying," is generally "not strong evidence of nonobviousness." *Vandenberg v. Dairy Equip. Co.*, 740 F.2d 1560, 1567 (Fed. Cir. 1984); *Amazon, Inc. v. Barnesandnoble.com, Inc.*, 239 F.3d 1343, 1366 (Fed. Cir. 2001). In Hatch-Waxman cases, however, "evidence of copying … is *not probative of nonobviousness* because a showing of bioequivalence is required for FDA approval." *Bayer*, 713 F.3d at 1377. In other words, generic manufacturers are *supposed to copy* branded drugs, 21 U.S.C. §§355(b)(2), 355(j); 35 U.S.C. §271(e)(2), under Congress' policy "to bring low-cost, generic *copies* of [new] drugs to market." *Andrx Pharms., Inc. v. Biovail Corp.*, 276 F.3d 1368, 1371 (Fed. Cir. 2002). When a generic competitor copies a *patented manufacturing process*, as opposed to the drug itself, that may be relevant because the Hatch-Waxman Act only requires copying drugs. *Merck Sharp & Dohme Corp. v. Hospira, Inc.*, 874 F.3d 724, 731 (Fed. Cir. 2017).

Here, the district court erroneously credited evidence that Teva copied the drug—*i.e.*, that Teva used the property of Teva product property of Teva product. The court believed Teva was not *required*

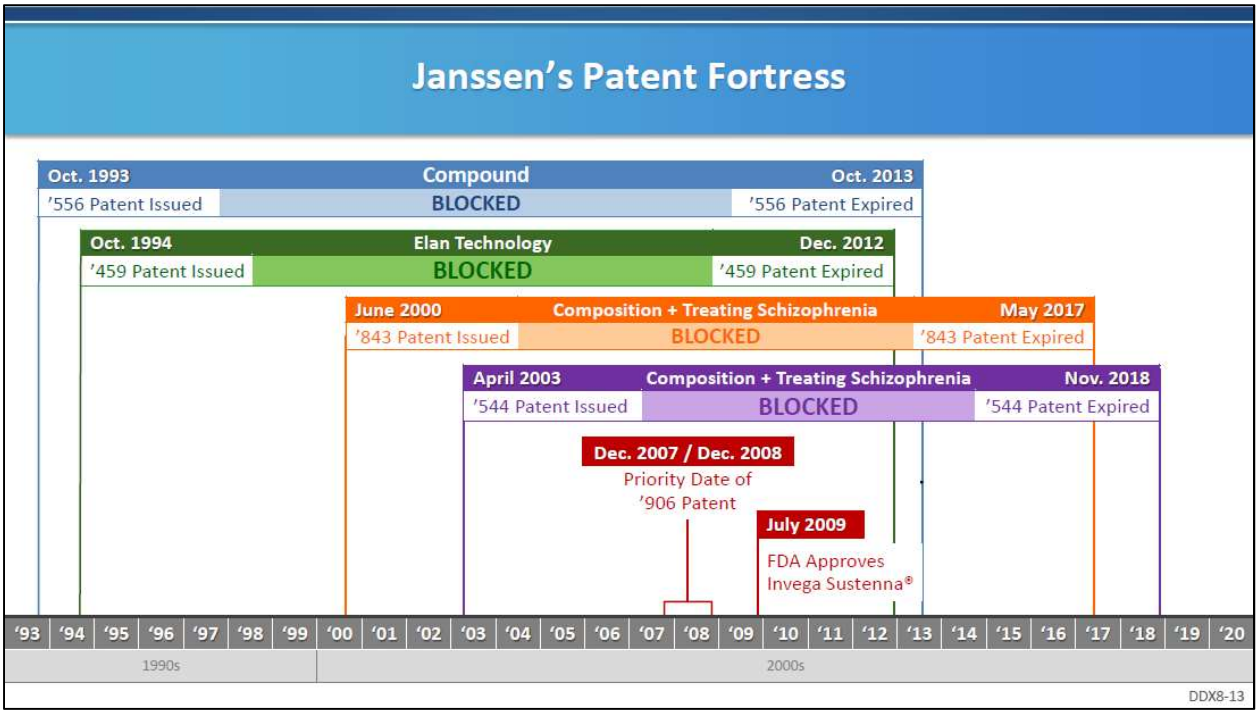
to use the property of Teva product, and that doing so was evidence of non-obviousness of Janssen's affected claims. Appx102-103. It was undisputed, however, that FDA approval *required* Teva's product to be bioequivalent to Janssen's. Appx11616(3-5). It is also undisputed that an intramuscular LAI's property of Teva product is a result-effective variable that determines the drug's bioavailability. Appx13239(3:52-55); Appx10291(6-19) ("if you wanted to impart changes reference to property reference to property"); Appx11777(1777:3-5). Indeed, Janssen filed a citizen's petition with the FDA to require particle-size measurements for all Invega Sustenna generics. Appx13151-13152. property in this case is thus not separable from the bioequivalence requirement in the way a manufacturing process might be, and the district court erred to the extent it placed even "some limited" weight on "copying." Appx103.

4. The District Court Misapplied the Law on Blocking Patents.

If a patented product is "commercially successful" and meets a "long-felt" but unmet demand, the patentee may urge the inference that the claims were not obvious. Otherwise, the logic goes, someone else would have developed the invention sooner and reaped the commercial

rewards. However, precedent recognizes that "blocking patents" may undermine or refute that inference. *Acorda Therapeutics, Inc. v. Roxane Lab'ys, Inc.*, 903 F.3d 1310, 1337-42 (Fed. Cir. 2018); *Galderma*, 737 F.3d at 740. When the patentee's other patents legally block others from market entry, "the inference of non-obviousness of the asserted claims, from evidence of commercial success, is weak." *Galderma*, 737 F.3d at 740.

The evidence of Janssen's blocking patents was unusually powerful here. The '906 patent's critical date is 2007. *For the previous fourteen years*, to *1993*, Janssen's Patent No. 5,254,556 blocked anyone else from making, using, offering to sell, selling or importing the paliperidone palmitate compound *at all*. As shown at trial in the slide below, between 1993 and 2007, Janssen continued to accumulate patents further fortifying its exclusive rights to paliperidone palmitate.



By 2007, Janssen's patent coverage included **(1)** paliperidone esters including paliperidone palmitate (5,254,556, Appx13282-13292); **(2)** aqueous paliperidone palmitate formulations (6,077,843, Appx13293-13298); and **(3)** aqueous nanoparticle paliperidone palmitate formulations (the '544 patent).

Those patents' scope and terms were not meaningfully disputed at trial. Teva thus argued the simple point that because only Janssen was legally permitted to develop Invega Sustenna, Janssen's blocking patents undermined any inference that might otherwise arise from Invega's "commercial success" or "long-felt need." *E.g.*, Appx12684-12685(2738:24-2739:22).

The district court's reasons for rejecting that point cannot withstand scrutiny. Appx110-114. The court faulted Teva's expert testimony (Hofmann) because he relied in part on another expert's testimony (Wermeling, Teva's technical expert) for the precise scope of Janssen's blocking patents.[6] The court took issue with Wermeling's deposition testimony that he could not then recall reviewing some of the blocking patents—which the court said "considerably weaken[ed] the probative value of *Mr. Hofmann's testimony*." Appx112. That "gotcha" point is irrelevant and does not make the scope of Janssen's blocking patents subject to meaningful dispute. There was no such dispute. And Hofmann's understanding of the blocking patents' scope was based not only on Wermeling's opinions, but also Janssen's expert's testimony, Janssen listing of those patents in the Orange Book, and Janssen's FDA submissions.[7]

The district court also remarked that it was "possible to practice Claim 2 of the '906 patent… without infringing the claims of the '544 and '843 patents." Appx112. That gets the analysis backward. Whether it

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[6] Appx12744(2-6); Appx12747(6-10); Appx12748-12749(2802:24-2803:10); Appx12750(9-16); Appx12758(18-22); Appx12759(11-16).

[7] Appx12742-12744(2796:20-2798:6); Appx12746-12747(2800:21-2801:10); Appx12748-12749(2802:24-2803:10); Appx12749-12750 (2803:25-2804:22); Appx12756(5-10).

was possible to infringe claim 2 with a product other than Invega Sustenna is irrelevant to the blocking question here. Janssen relied on *Invega Sustenna* sales as evidence of "commercial success." Janssen's '544 and '843 patents (orange and purple bars on the slide above) blocked others from producing *Invega Sustenna*, thus undermining any inference that *Invega Sustenna*'s "commercial success" is somehow evidence of non-obviousness. The court's comment also ignores that the *'556 and '459 patents* (blue and green bars above) would still have blocked competition until 2013.

Finally, the court found "little, if any, disincentives to innovate" in light of the Hatch-Waxman Act's safe harbor provision, 35 U.S.C. §271(e)(2), the existence of "paliperidone palmitate" clinical trials, and competitor activity relating to *risperidone*. Appx113-114. If the safe-harbor provision were sufficient to negate blocking patents, cases like *Acorda* and *Galderma* would have been decided differently. "Risperidone" activity is irrelevant. That Janssen may have tolerated paliperidone clinical trials by others may be relevant, but not independently sufficient to negate the fourteen-year blocking effect of Janssen's patents before 2007. To the extent the district court placed any significant weight on Janssen's

"long-felt need" or "commercial success" evidence, that was legal error and cannot support the judgment.

II. The No-Indefiniteness Judgment Should Be Reversed as to the "Average Particle Size" Claims (19-21).

Every patent's claims must "particularly point[] out and distinctly claim[] the subject matter which the [patentee] regards as the invention." 35 U.S.C. §112(b). The "claims, viewed in light of the specification and prosecution history," must "inform those skilled in the art about the scope of the invention with reasonable certainty." *Nautilus, Inc. v. Biosig Instruments, Inc.*, 572 U.S. 898, 910 (2014). Put differently, claims "must provide objective boundaries for those of skill in the art." *Interval Licensing LLC v. AOL, Inc.*, 766 F.3d 1364, 1371 (Fed. Cir. 2014).

On remand from the Supreme Court in *Teva v. Sandoz*, this Court held that a claim fails that test and is indefinite when it recites a measured property, but the intrinsic evidence does not convey with reasonable certainty *how* to measure that property. 789 F.3d at 1344-45. There, the claims recited a polymer "having a *molecular weight* of about 5 to 9 kilodaltons." "Three different measures of molecular weight" existed, "[e]ach measure is calculated in a different manner," and the different measures

"have different values" in a typical sample. *Id.* at 1338. Where the specification and prosecution history did not convey to a skilled artisan which measure to use, the claims were indefinite, and the district court's decision upholding the claims was reversed. *Id.* at 1344-45.

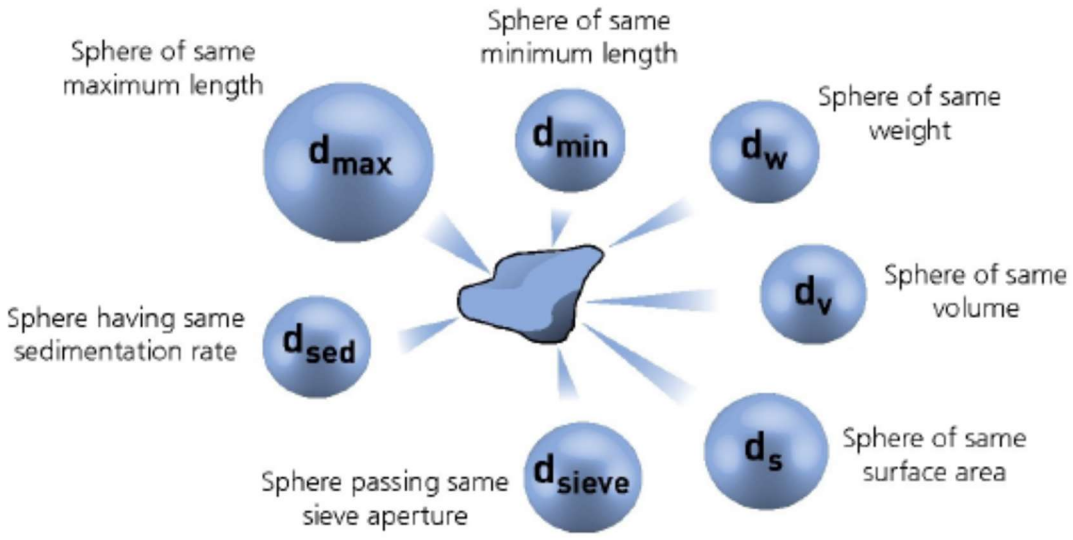
Dow applied the same principle to hold that claims reciting "a slope of strain hardening coefficient greater than or equal to 1.3" were indefinite. 803 F.3d at 631. Although the written description provided an equation to calculate "slope of strain hardening coefficient," the claims were "indefinite because the patent fails to teach with reasonable certainty *where and how* the 'slope of strain hardening' should be measured." *Id.* at 633. Experts testified regarding four measurement methods, but the intrinsic evidence did not discuss those methods, nor "provide[] guidance as to which method should be used, or even whether the possible universe of methods is limited to these four methods." *Id.* at 634. The question for the Court was thus "whether the existence of multiple methods leading to different results without guidance in the patent or the prosecution history as to which method should be used renders the claims indefinite." *Id.* The answer was yes, and the district court judgment upholding the claims was reversed.

So it is here. The "average particle size" claims here are no different from the "molecular weight" claims *Teva v. Sandoz*, or the "slope of strain hardening" claims in *Dow*. Claims 19-21 all recite that "156 mg/ml of the paliperidone palmitate ha[s] *an average particle size (d50) of from about 1600nm to about 900nm*." The '906 patent's written description, in turn, acknowledges that multiple measurement techniques exist, stating any "art-known conventional techniques" can be used to measure particle size, including "sedimentation field flow fractionation, photon correlation spectroscopy or disk centrifugation" as well as laser diffraction. Appx162(7:32-38); Appx165(14:51-53). The intrinsic evidence undisputedly provides no details regarding acceptable parameters, instruments, or procedures for any technique.

The district court's statement that "different methods or expressions of measurement lead to essentially identical values," Appx134, is simply wrong. The trial evidence refutes that statement and confirms the opposite: different methods and measurements of "average particle size" produce wildly different results because they measure different properties in different ways. *See* Appx10597-10598(597:13-598:4); Appx10613(13-16); Appx16434.

Importantly, paliperidone palmitate particles (like most particles) are irregularly shaped, and known measurement techniques do not measure individual particles. Instead, **(1)** measurements that correlate in some way with particle size are taken from a sample, and **(2)** "average particle size" is *estimated* in part by treating the particles as if they were perfect spheres, where "size" is the diameter of an "equivalent sphere." Appx16306; Appx16318. Skilled artisans may use any of at least *seven* different properties of the irregularly-shaped particles to derive different "equivalent spheres": **(1)** maximum length, **(2)** minimum length, **(3)** weight, **(4)** volume, **(5)** surface area, **(6)** sieve aperture, and **(7)** sedimentation rate. Appx16306.

As a publication by the "Mastersizer" manufacturer explains, "different measurement techniques use different equivalent sphere models and therefore will not necessarily give exactly the same result for the particle diameter." Appx16306. That same publication provides the illustration below, with an irregularly-shaped particle at the center, surrounded by seven "equivalent spheres" of different sizes depending on which property is used to model the spheres.



Appx16306

In this case, Janssen measured its particle size for the FDA using adjective conventional devices, and obtained adjective results results results. The "Mastersizer" uses laser diffraction, Appx20632, and an undisclosed proprietary algorithm with undisclosed equivalent-sphere modeling to estimate particle size. The "Coulter" uses a "hybrid" of "laser diffraction" and another technology ("Polarization Intensity Differential Scattering"), Appx20631; Appx11555(5-17); Appx10654(2-24), and a different undisclosed proprietary algorithm to estimate average particle size.

Janssen obtained some results details of results details of results used the Coulter or Mastersizer. Appx20632 details of results

[redacted] *see also* Appx20633 ("when comparing the average diameters, those generated by [redacted]"). In fact, Janssen submitted [redacted] to the FDA [redacted] Appx13179-13180 [redacted] Janssen's experts testified that Coulter's different technology was "a problem," Appx11555(1555:5-17), and further testing would be necessary to figure out which measurement (Coulter or Mastersizer) was right. Appx11555-11556(1555:19-1556:3); Appx11556-11558(1556:23-1558:9).

Teva also presented unrebutted evidence that even when Janssen and Teva used the same type of device, they obtained different results. Janssen and Teva both measured the same batch of paliperidone palmitate (FIB3801) using a Mastersizer. Appx10609-10610(609:19-610:19). Janssen measured 1100 nm (inside the claimed range), *id.*; Appx16413, and Teva measured 700 nm (outside the claimed range), Appx10609-10610(609:19-610:19); Appx16498.

The district court said nothing about the different ways to estimate average particle size or different properties used to model "equivalent

spheres." Instead, it broadly dismissed the trial evidence as "equipment error" or attributable to "a defective device," Appx132 &n.52, and "note[d] that both experts testified … there were no issues with measuring d50." Appx134-135. The "equipment error" and "defective device" statements are unsupported, and the "no issues" testimony is irrelevant.

Coulter is a standard, common instrument for measuring particle size. *See* Appx10612(15-23); Appx13861-13862 (Janssen's expert's text-book describing Coulter as a "popular instrument for measuring the volume of particles"); Appx20630-20631 (Janssen used Coulter "in support of clinical and preclinical trials."). That Janssen measuring technique evaluation of meaurement technique and *internally* concluded evaluation of meaurement technique, Appx20635, says nothing about whether a POSA reading the '906 patent would know whether the claims did or not cover Coulter measurements.

As to the "no issues" testimony, as explained, measurements measurements Teva "had no issues" measuring particle size and reporting particle size to the FDA because Teva identified and used a procedure the FDA accepted. Appx19799-

Confidential Material Redacted

19812. That has no bearing on whether those measurements are inside or outside the scope of claims 19-21, which is unknowable here.

Here, as in *Teva v. Sandoz* and *Dow*, claims 19-21 of the '906 patent recite an element that has multiple different meanings to a POSA. Average particle sizes can be estimated by measuring different properties by different methods, "leading to different results without guidance in the patent or the prosecution history as to which method should be used renders the claims indefinite." *Dow*, 803 F.3d at 634. Here, as in *Teva v. Sandoz* and *Dow*, the claims are indefinite and the district court's contrary judgment must be reversed.

CONCLUSION

The judgments should be reversed, or vacated and remanded.

May 13, 2022

Respectfully submitted,

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(signed with permission)

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ADDENDUM

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

JANSSEN PHARMACEUTICALS, INC. and JANSSEN PHARMACEUTICA NV, *Plaintiffs*, v. MYLAN LABORATORIES LIMITED, *Defendant*.	Civil Action No. 2:19-cv-16484-CCC-LDW

FINAL JUDGMENT

NOW THEREFORE, IT IS HEREBY ORDERED, ADJUDGED, AND DECREED that:

1. This Court has jurisdiction over Plaintiffs Janssen Pharmaceuticals, Inc. and Janssen Pharmaceutica NV (collectively, "Janssen") and Defendant Mylan Laboratories Limited ("Mylan") and the subject matter of this action.

2. Pursuant to the Stipulation and Order in this Action entered May 28, 2021 (D.I. 71 ¶ 4), Janssen and Mylan are bound by the Final Judgment in *Janssen Pharmaceuticals, Inc. v. Teva Pharmaceuticals USA, Inc.*, Civil Action No. 2:18-cv-00734 ("the Teva Action") (Teva Action, D.I. 273) as if Mylan had fully participated in the Teva Action.

3. Therefore, for the reasons set forth in the Court's Opinion in the Teva Action dated October 8, 2021 (Teva Action, D.I. 266, 271), and as reflected in the Court's Order of the same date (Teva Action, D.I. 267), Final Judgment is entered in favor of Janssen and against Mylan on all claims and counterclaims with respect to infringement and validity of United States Patent No. 9,439,906 ("the '906 patent") and Mylan's products that are the subject of ANDA No. 213124.

4. Pursuant to 35 U.S.C. § 271(e)(4)(A), the effective date of any approval of Mylan's ANDA No. 213124 shall be no earlier than the date of expiration of the '906 patent (currently

January 26, 2031).

5. Pursuant to 35 U.S.C. § 271(e)(4)(B), Mylan and its affiliates, successors, partners, officers, agents, servants, employees, and attorneys, and other persons or entities in active concert or participation with any of them, are hereby enjoined from offering to sell or selling within the United States the products that are the subject of ANDA No. 213124 until no earlier than the expiration of the '906 patent (currently January 26, 2031). As used in this paragraph 5, "offering to sell" means to make an "offer for sale" or "offer to sell" as those terms are defined in 35 U.S.C. § 271(i).

6. In accordance with 21 C.F.R. § 314.107(e), Mylan shall submit a copy of this Final Judgment to the FDA within fourteen (14) days of the date of entry of this Final Judgment by the Court.

7. For the avoidance of doubt, this Final Judgment does not address and shall have no effect on any regulatory exclusivities to which Janssen may become entitled after its entry.

8. Each party shall bear its own fees and costs.

9. This is a final, appealable judgment.

IT IS SO ORDERED, on this 22 day of December, 2021

Hon. Claire C. Cecchi
United States District Judge

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

JANSSEN PHARMACEUTICALS, INC. and JANSSEN PHARMACEUTICA NV, *Plaintiffs*, v. TEVA PHARMACEUTICALS USA, INC., *Defendant*.	Civil Action No. 2:18-00734 (CCC)(LDW)

FINAL JUDGMENT

NOW THEREFORE, IT IS HEREBY ORDERED, ADJUDGED, AND DECREED that:

1. This Court has jurisdiction over Plaintiffs Janssen Pharmaceuticals, Inc. and Janssen Pharmaceutica NV (collectively, "Janssen") and Defendant Teva Pharmaceuticals USA, Inc. ("Teva")[1] and the subject matter of this action.

2. For the reasons set forth in the Court's Opinion dated October 8, 2021 (D.I. 266), and as reflected in the Court's Order of the same date (D.I. 267), Final Judgment is entered in favor of Janssen and against Teva on all claims and counterclaims with respect to infringement and validity of United States Patent No. 9,439,906 ("the '906 patent") and Teva's products that are the subject of ANDA No. 211149.

3. Pursuant to 35 U.S.C. § 271(e)(4)(A), the effective date of any approval of Teva's ANDA No. 211149 shall be no earlier than the date of expiration of the '906 patent (currently January 26, 2031).

[1] Pursuant to the Stipulation and Order Dismissing Without Prejudice Defendant Teva Pharmaceutical Industries Ltd. and Amending Caption in the Action to Reflect Same (D.I. 26 ¶ 2), Teva Pharmaceutical Industries, Ltd. is bound by this Final Judgment, as well as any Judgment, Order, or decision, including any injunction, rendered as to Teva in this Action.

4. Pursuant to 35 U.S.C. § 271(e)(4)(B), Teva and its affiliates, successors, partners, officers, agents, servants, employees, and attorneys, and other persons or entities in active concert or participation with any of them, are hereby enjoined from commercially manufacturing, using, offering to sell, or selling within the United States, or importing into the United States, the products that are the subject of ANDA No. 211149 until no earlier than the expiration of the '906 patent (currently January 26, 2031).

5. For the avoidance of doubt, this Final Judgment does not address and shall have no effect on any regulatory exclusivities to which Janssen may become entitled after its entry.

6. In accordance with 21 C.F.R. § 314.107(e), Teva shall submit a copy of this Final Judgment to the FDA within fourteen (14) days of the date of entry of this Final Judgment by the Court.

7. Pursuant to Fed. R. Civ. P. 54, L. Civ. R. 54.1, and 28 U.S.C. § 1920, Janssen may seek its costs, subject to Paragraphs 8 and 9, in an amount to be determined by the Clerk of the Court.

8. In the event that a party appeals this Final Judgment, any motion for attorney fees and/or costs, including any bill of costs or motion that this case is exceptional under 35 U.S.C. § 285, shall be considered timely if filed and served within 60 days after the expiration of the time to petition for certiorari to the United States Supreme Court or, if the appeal is withdrawn or dismissed, within 60 days after such withdrawal or dismissal.

9. In the event that no party appeals this Final Judgment, any motion for attorney fees and/or costs, including any bill of costs or motion that this case is exceptional under 35 U.S.C. § 285, shall be considered timely if filed and served within 60 days after the expiration of the time for filing a notice of appeal under Fed. R. App. P. 3 and 4.

10. This is a final, appealable judgment.

IT IS SO ORDERED, on this 16 day of November, 2021

Hon. Claire C. Cecchi
United States District Judge

UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

JANSSEN PHARMACEUTICALS, INC. and JANSSEN PHARMACEUTICA NV, Plaintiffs, v. TEVA PHARMACEUTICALS USA, INC., Defendant.	Civil Action No.: 18-734 **OPINION**

CECCHI, District Judge.

This patent case was brought by Plaintiffs Janssen Pharmaceuticals, Inc. and Janssen Pharmaceutica NV (collectively, "Plaintiffs" or "Janssen") against Defendant Teva Pharmaceuticals USA, Inc. ("Defendant" or "Teva"). This action specifically concerns the validity of Claims 1–21 of U.S. Patent No. 9,439,906 (the "'906 Patent" or the "Patent-in-Suit"). ECF No. 133 ("Final Pretrial Order") at 2. The '906 Patent covers "a dosing regimen for administering paliperidone palmitate to a psychiatric patient in need of treatment for schizophrenia, schizoaffective disorder, schizophreniform disorder, or other psychotic disorders." *Id.*

The Court held a two-week bench trial in this matter that began on October 13, 2020, and concluded on October 30, 2020. ECF Nos. 135–37, 140–41, 145–49, 151. The parties submitted post-trial briefing and proposed findings of fact and conclusions of law in December 2020. ECF Nos. 164 ("Pls. Br."), 165 ("PFOF"), 167 ("Def. Br."), 167-1 (*corrected at* 168-1 ("DFOF")). On January 8, 2021, the parties submitted responsive briefs. ECF Nos. 188 ("Pls. Reply Br."), 189 ("Def. Reply Br."). Closing arguments were held on March 5, 2021. ECF No. 199.

In a letter dated December 5, 2017, Teva notified Janssen that it had submitted Abbreviated

New Drug Application ("ANDA") No. 211149 to the United States Food and Drug Administration ("FDA") "seeking FDA approval to engage in the commercial manufacture, use, sale, offer for sale in, and/or importation into the United States of generic paliperidone palmitate extended-release injectable suspension products . . . prior to the expiration of the 906 Patent." Final Pretrial Order at 2. Defendant does not contest infringement of the '906 Patent. *Id.* Therefore, the only the issue for this Court to decide is whether the Patent-in-Suit is invalid based on the following legal principles: (1) obviousness; (2) lack of written description; and (3) indefiniteness.[1] *Id.* at 2–3.

This Opinion constitutes the Court's findings of fact and conclusions of law pursuant to Federal Rule of Civil Procedure 52(a). The findings of fact are based on the Court's observations and credibility determinations of the witnesses who testified at trial, and a thorough review of all the evidence admitted at trial. While the Court has reviewed all of the evidence presented, given the length of the trial record, the Court includes references only to the evidence most pertinent to its analysis.[2] For the reasons set forth below, the Court finds that the Patent-in-Suit is not invalid.

I. BACKGROUND

A. Parties

Plaintiff Janssen Pharmaceuticals, Inc. is a corporation organized and existing under the laws of the Commonwealth of Pennsylvania, and has its principal place of business at 1125 Trenton-Harbourton Road, Titusville, New Jersey 08560. *Id.* at 4. Plaintiff Janssen Pharmaceutica

[1] Post-trial, in July 2021, Teva filed a motion to amend pursuant to Federal Rule of Civil Procedure 15(b)(2), asking the Court to deem its pleadings amended with a count for patent invalidity due to incorrect inventorship under 35 U.S.C. § 102(f). ECF No. 244. The Court will discuss this motion and the potential additional invalidity challenge later in this Opinion.

[2] At the request of the Court, the parties submitted motions shortly after trial presenting their arguments on certain evidentiary issues. ECF Nos. 152–153. All relevant evidentiary issues raised in that briefing, any *in limine* motions, and elsewhere (*e.g.*, ECF No. 98), are resolved in this Opinion.

NV is a corporation organized and existing under the laws of Belgium, and has its principal place of business at Turnhoutseweg, 30, B-2340 Beerse, Belgium. *Id.* Janssen Pharmaceutica NV "is the owner of the entire right, title, and interest in and to the '906 Patent." *Id.* at 5. Defendant Teva is a corporation organized and existing under the laws of Delaware, and has its principal place of business at 1090 Horsham Road, North Wales, Pennsylvania 19454. *Id.* at 4.

B. Background of the Invention

The dosing regimens at issue in this case provide detailed information concerning the use of paliperidone palmitate to treat schizophrenia and other psychotic disorders. To this end, the '906 Patent discloses unique combinations of dose amounts, dosing schedules, injection sites, and formulation properties. PFOF ¶ 7.[3] The main dosing regimen contained in Claim 2 consists of a 150 mg-eq.[4] first loading dose of paliperidone palmitate in the deltoid muscle on the first day of treatment, a second loading dose of 100 mg-eq. in the deltoid muscle during the sixth to tenth day of treatment, and successive monthly (± 7 days) maintenance doses of 25 mg-eq. to about 150 mg-eq. in either the deltoid or gluteal muscle. '906 Patent (DTX-1/PTX-1) col. 32:11–36. The main dosing regimen for patients with renal impairment contained in Claim 10 consists of a loading dose from about 75 mg-eq. in the deltoid muscle on the first day of treatment, a second loading dose from about 75 mg-eq. in the deltoid muscle on the sixth to tenth day of treatment, and successive monthly (± 7 days) maintenance doses of 25 mg-eq. to about 75 mg-eq. in either the deltoid or gluteal muscle. *Id.* col. 33:3–27.

[3] The parties have agreed to a representative set of claims for purposes of this matter. Final Pretrial Order at 9. Claim 2 of the '906 Patent represents Claims 1, 3–7, and 15; Claim 10 represents Claims 8–9; Claim 13 represents Claims 11–12, 14, and 16; Claim 20 (as it depends from Claims 1 or 8) represents no other claims; and Claim 21 (as it depends from Claims 1 or 8) represents Claims 17–19. *Id.* These Claims will be collectively referred to as the "Representative Claims."

[4] Doses of paliperidone palmitate are typically expressed in terms of their equivalent amount of paliperidone (expressed as "milligram-equivalent" or "mg-eq.") rather than their actual weight. PFOF ¶ 6.

This section will first provide the scientific background of the claimed invention. Next, the Court will provide the relevant research and patent history for the Patent-in-Suit.

1. Scientific Background

Schizophrenia is a chronic psychotic disorder that affects approximately one percent of the world's population. DFOF ¶ 52; PFOF ¶ 11. The disorder is most commonly characterized by "disorganized behavior and speech, delusions, and hallucinations." PFOF ¶ 11. Schizophrenia often manifests "in young people between the ages of 15 and 30," and is typically diagnosed after an individual suffers an acute psychotic episode. *Id.* ¶ 12; Trial Tr. (Kohler) at 1883:4–12. Antipsychotic medication is the main form of treatment for schizophrenia, and its aim is to achieve remission such that a person with schizophrenia can manage their symptoms and function independently. DFOF ¶¶ 53, 55; PFOF ¶ 12. There is currently no cure for schizophrenia, and each psychotic episode inflicts permanent damage upon the brain and reduces the chances of achieving remission. PFOF ¶¶ 12–13.

Schizophrenia is generally treated with antipsychotic drugs which have been available since the 1950s. DFOF ¶ 54; PFOF ¶ 15. These drugs are typically administered orally or as long-acting injectable formulations ("LAI"), sometimes referred to as a "depot." DFOF ¶¶ 56–57; PFOF ¶¶ 14–15. Schizophrenia is challenging to treat because the symptoms of the disease make it difficult for patients to comply with their prescribed treatment, particularly when it comes to daily oral antipsychotics. DFOF ¶ 57; PFOF ¶ 14. When patients stop taking their medicine or miss a dose, they often have a relapse in the form of an acute psychotic episode, which can set off a cycle of worsening symptoms, additional missed treatment, and possibly institutionalization. *Id.*

"First-Generation" LAIs developed in the 1950s include "Prolixin (fluphenazine) decanoate, Prolixin (fluphenazine) enanthate, and Haldol (haloperidol) decanoate." PFOF ¶ 15. These LAIs were accompanied by serious mental side effects such as dullness and cognitive

impairment. *Id.* ¶ 16; *see also* DFOF ¶ 497. They were also associated with extrapyramidal symptoms ("EPS") consisting of serious motor impairments, painful muscle contractions, tremors, and stiffness. PFOF ¶ 16; *see also* DFOF ¶¶ 497–498. Due to the severe mental and physical side effects associated with First-Generation LAIs, they were generally restricted to institutionalized patients who could not function in society. PFOF ¶ 17.

"Second-Generation" antipsychotics, developed in the 1980s and 1990s, were viewed as a major improvement from First-Generation antipsychotics because they had less frequent and less severe side effects (including EPS). *Id.* ¶ 19. Most of the Second-Generation antipsychotic drugs were administered orally, with Janssen's Risperdal Consta serving as the only Second-Generation LAI on the market for some period of time. *Id.* Risperdal Consta, however, requires oral supplementation for the first three weeks of treatment and provides only two weeks of therapeutic benefits, making biweekly injections necessary. *Id.* ¶ 20.

Janssen sought to improve upon these limitations, and eventually received FDA approval for Invega Sustenna in 2009. *Id.* ¶ 60. Invega Sustenna is seen as a vastly superior product to Risperdal Consta due to its unique dosing regimen consisting of high loading dose injections to initiate treatment and monthly maintenance injections thereafter. *Id.* ¶ 175–76. The dosing regimen does not require oral supplementation, is initiated in a uniform manner, and has led to important benefits such as improved treatment adherence and reduced risk of relapse. *Id.* ¶¶ 176, 190. Invega Sustenna is a "blockbuster" drug, and since 2013, it has accounted for the largest revenue share in the LAI antipsychotic market, with net sales of $1.7 billion in 2019 alone. *Id.* ¶¶ 187–88. When dosed according to its label, Invega Sustenna practices the claims of the '906 Patent. *Id.* ¶ 171.

2. Research and Patent History

Invega Sustenna was developed over the course of more than a decade, in a process

involving multiple stages of research, numerous clinical trials, and various unexpected setbacks. *Id.* ¶¶ 26, 36. The initial preclinical stage of the process consisted of formulation development and animal research. *Id.* Following the preclinical stage, Janssen began Phase I clinical trials. During Phase I, Janssen studied the formulation of paliperidone palmitate to be used in the drug, eventually choosing formulation F13. *Id.* ¶ 27. Janssen also studied single versus multiple-dose regimens, and deltoid versus gluteal injection sites in Phase I. *Id.* ¶¶ 27–29. In the BEL-7 Phase I clinical trial,[5] Janssen observed better results with a loading dose regimen of double doses on day 1 followed by monthly maintenance doses, and chose this regimen for further development. *Id.* ¶ 28. In the USA-3 Phase I clinical trial, Janssen observed that injections in the deltoid led to "higher peak plasma concentrations compared to gluteal injections." *Id.* ¶ 29. Based on these findings, Janssen used the gluteal muscle for all injections in Phase II clinical trials because higher plasma concentrations present a greater risk of severe side effects. *Id.*

After seven years of Phase I clinical trials, Janssen began Phase II clinical trials in October 2003. *Id.* ¶ 30. These clinical trials were designed to measure efficacy, and Janssen was excited by the results of its SCH-201 Phase II clinical trial that indicated rapid efficacy compared to placebo by day 8 of treatment. *Id.* ¶¶ 30–31. As Dr. An Vermeulen, a named inventor of the '906 Patent, testified at trial, this was the "first study to demonstrate efficacy of" paliperidone, it "confirmed safety and tolerability," and "efficacy was achieved quickly within the first week." Trial Tr. (Vermeulen) at 776:8–12; '906 Patent (DTX-1/PTX-1). The Court credits Dr. Vermeulen's trial testimony, and notes that she is currently an internal consultant in the Quantitative Sciences Consulting Group at Janssen. Trial Tr. (Vermeulen) at 744:3–6.

[5] The Court notes that this Research and Patent History section only discusses a subset of the most relevant studies that were conducted during the development of Invega Sustenna.

In Phase III, Janssen developed three different trials to build on the SCH-201 trial. PFOF ¶ 32. The PSY-3004 and PSY-3003 trials compared equal doses of paliperidone palmitate in the F11 and F13 formulations, with all injections given in the gluteal muscle on days 1/8/36/64, and efficacy measured by assessing changes in PANSS scores. *Id.* ¶ 32. PANSS refers to the Positive and Negative Syndrome Scale, a questionnaire administered to a patient asking about the symptoms of schizophrenia. *Id.* ¶ 30. PSY-3002 was a non-inferiority study which tested the F11 and F13 formulations of paliperidone palmitate against Risperdal Consta in 749 patients. *Id.* ¶ 33. Subjects in this study received 50 mg-eq. of paliperidone palmitate in the gluteal muscle on days 1 and 8, followed by either 25, 50, 75, or 100 mg-eq. doses monthly. *Id.*

All three trials were unexpected failures. *Id.* ¶¶ 36, 52. The results of PSY-3004 came in May 2006 and were a major disappointment to Janssen as they showed no effectiveness in subjects in the United States. *Id.* ¶ 34. Next, the PSY-3003 results arrived in August 2006 and brought additional bad news as that study failed to demonstrate superiority of any dose of paliperidone palmitate in the United States when compared to placebo. *Id.* ¶ 35. The results of PSY-3002, which were also disappointing to Janssen, did not arrive until later and are discussed below.

In response to the disappointing results of PSY-3004 and PSY-3003, Janssen assembled a task force of clinical, pharmaceutical, preclinical, bioanalytical, clinical pharmacology, and pharmacometric[6] specialists to understand the results from these studies and formulate a path forward. *Id.* ¶ 38. The task force, relying in large part on population pharmacokinetic modeling

[6] Pharmacometrics is a discipline that applies advanced modeling techniques to make sense of data across entire populations concerning pharmacokinetics (how the body handles a drug), taking into account the patient-specific characteristics that lead to variability in individual exposure profiles. PFOF ¶ 25. This work requires patient data and patient-specific characteristics to build a mathematical model with both explanatory and predictive power. *Id.* The goal of this modeling is to identify dosing regimens that are effective for the majority of subjects. *Id.*

done by Dr. Vermeulen, found that body mass index had an impact on the levels of paliperidone palmitate in the blood and found that choice of injection site had a significant effect as well. *Id.* ¶ 42. In order to overcome these issues, the task force recommended a dosing regimen of 150 mg-eq. in the deltoid muscle on day 1, followed by a dose of 25, 50, 100, or 150 mg-eq. in the deltoid or gluteal muscle on day 8, and monthly maintenance doses. *Id.* ¶ 43.

This new dosing regimen was tested in the PSY-3007 and PSY-3006 Phase III clinical trials. *Id.* ¶ 44. Dr. Srihari Gopal, a senior director in the Psychiatry Department at Janssen Research and Development, LLC, led the design of these new trials. *Id.* ¶ 44; Final Pretrial Order at 29. PSY-3007, which began in March 2007, compared a dosing regimen of 150 mg-eq. in the deltoid muscle on day 1 followed by equal doses of either 25, 100, or 150 mg-eq. in the gluteal or deltoid muscle against a placebo. PFOF ¶ 44. PSY-3006, which began the same month, was a non-inferiority study comparing the F13 formulation of paliperidone palmitate to Risperdal Consta. *Id.* ¶ 45. Patients in this study received 150 mg-eq. in the deltoid muscle on day 1 and 50 mg-eq. on day 8 in the gluteal or deltoid muscle, followed by monthly maintenance doses. *Id.* After the results of PSY-3002 finally came back in May 2007 and failed to demonstrate non-inferiority to Risperdal Consta, Janssen decided to modify the PSY-3006 study to change the day 8 dose from 50 mg-eq. in the gluteal or deltoid muscle to 100 mg-eq. in the deltoid muscle. *Id.* ¶¶ 52–53. Around the same time, Dr. Mahesh Samtani, currently a senior scientific director at Janssen,[7] took over for Dr. Vermeulen (Dr. Vermeulen had been promoted) and further developed the population pharmacokinetic model. *Id.* ¶ 48; Trial Tr. (Samtani) at 1342:6–7. Dr. Samtani's new model ran simulations of different dosing regimens by varying sequencing, dose amount, and

[7] As discussed later in this Opinion, Janssen asserts that Dr. Samtani and Dr. Gopal should be added as named inventors of the '906 Patent.

administration site, to determine if Janssen's preferred dosing regimen could achieve rapid efficacy without oral supplementation in as many individuals as possible without risking severe side effects. PFOF ¶ 50.

While awaiting the results of PSY-3007 and PSY-3006, Janssen began the FDA approval process based in large part on Dr. Samtani's modeling. *Id.* ¶¶ 56–57. In October 2007, Janssen submitted a New Drug Application seeking approval for a 100/100 mg-eq., day 1/day 8 deltoid muscle dosing regimen because it had Phase III safety data available for this regimen. *Id.* ¶ 57. The FDA responded in August 2008 and suggested that Janssen consider a lower dosing regimen of 75 or 100 mg-eq. on day 1, followed by 75 or 100 mg-eq. on day 8. *Id.* ¶ 58. Janssen countered the FDA's recommendation, using Dr. Samtani's models, as well as the PSY-3007 results received in the spring of 2008 and the PSY-3006 results received around July 2009, to show that the 150 mg-eq. day 1 and 100 mg-eq. day 8 dosing regimen (eventually claimed in the '906 Patent) resulted in more patients obtaining therapeutic levels of paliperidone by day 8. *Id.* ¶ 59–60. With this showing, the FDA approved Janssen's higher dosing regimen that Invega Sustenna practices in 2009. *Id.* ¶ 60. Janssen contends that this was a novel approach that went against the traditional dosing philosophy generally used for LAI antipsychotics at the time. *Id.* ¶ 58. [8]

C. Patent-in-Suit and Relevant Prosecution History

The '906 Patent, entitled "Dosing Regimen Associated With Long Acting Injectable Paliperidone Esters," issued on September 13, 2016, and expires on January 26, 2031. '906 Patent (DTX-1/PTX-1). The asserted claims generally relate to:

[8] The Court notes that the parties have different views regarding the development process of Invega Sustenna, as Janssen claims that "the extraordinary skill of Janssen's scientists" led to the project's success in spite of unexpected setbacks (Pls. Br. at 12), while Teva argues that "the alleged difficulties Janssen faced during development were avoidable" (Def. Br. at 55). Given these positions, further details on the drug development process will be discussed below.

> a dosing regimen for administering paliperidone esters to a psychiatric patient in need of treatment comprising administering intramuscularly in the deltoid a first loading dose from about 100 mg-eq. to about 150 mg-eq. of paliperidone as a paliperidone palmitate formulated in a sustained release formulation on the first day of treatment; administering intramuscularly a second loading dose from about 100 mg to about 150 mg-eq. of paliperidone as a paliperidone palmitate formulated in a sustained release formulation between about the 6th to 10th day of treatment; and administering intramuscularly in the gluteal a maintenance dose of about 25 to about 150 mg-eq. of paliperidone as a paliperidone ester in a sustained release formulation on between about the 34th and about the 38th day of treatment.

Id. col. 2:12–25. More specifically, the various claims of the '906 Patent provide details about the injection site, injection timing, and dosage amounts of paliperidone palmitate that should be used (Claim 2), alternative dosing regimens for renally impaired patients whose kidneys do not clear paliperidone as effectively as non-renally impaired patients (Claims 10 and 13), and precise characteristics of the paliperidone palmitate formulation that must be used (Claims 20 and 21). PFOF ¶¶ 7–9; *see also* '906 Patent (DTX-1/PTX-1).

On December 19, 2007, Janssen filed U.S. Provisional Application No. 61/014,918 (the "'918 Provisional"). PFOF ¶ 66. The '906 Patent claims the benefit of both the '918 Provisional and U.S. Provisional Application 61/120,276 filed on December 5, 2008. '906 Patent (DTX-1/PTX-1) col. 1:8–10. Janssen subsequently filed application number 12/337,144 on December 17, 2009, which eventually matured into the '906 Patent. Final Pretrial Order at 5. The '906 Patent then issued on September 13, 2016. '906 Patent (DTX-1/PTX-1).

II. ISSUES TO BE DECIDED

By Stipulation and Order dated June 8, 2020, Teva has agreed that for purposes of this lawsuit, it "will not contest that the making, using, offering to sell, or sale of Teva's Proposed Generic Products within the United States . . . would infringe and/or induce infringement of any valid Asserted Claim." ECF No. 88 at 2. Accordingly, the question before this Court is whether

the '906 Patent is invalid based upon Teva's asserted challenges.

III. DISCUSSION

Issued patents are presumed valid. *See* 35 U.S.C. § 282(a). To rebut this presumption, Defendant bears the burden of proving invalidity by clear and convincing evidence. *Titan Tire Corp. v. Case New Holland, Inc.*, 566 F.3d 1372, 1376 (Fed. Cir. 2009) ("Because of this presumption, an alleged infringer who raises invalidity as an affirmative defense has the ultimate burden of persuasion to prove invalidity by clear and convincing evidence, as well as the initial burden of going forward with evidence to support its invalidity allegation.").

A. Obviousness (35 U.S.C. § 103)

To prove that an asserted claim of a patent is invalid as obvious under 35 U.S.C. § 103, a patent challenger bears the burden of establishing by clear and convincing evidence that the "differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art." 35 U.S.C. § 103;[9] *see also Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1360–61 (Fed. Cir. 2007). A person of ordinary skill in the art will hereinafter be referred to as a "POSA." Obviousness is a question of law that is predicated on several factual inquiries. *See Graham v. John Deere Co. of Kansas City*, 383 U.S. 1, 17 (1966). Specifically, there are four basic factual inquiries that concern: (1) the scope and content of the prior art; (2) the level of ordinary skill in the art;[10] (3) the differences between the claimed subject matter and the prior art;

[9] The parties assert that the pre-America Invents Act version of 35 U.S.C. applies to the Patent-in-Suit. Final Pretrial Order at 2.

[10] Although the parties presented slightly different definitions of a POSA, they agree that any differences are immaterial. *See* Trial Tr. (Closing Argument) at 122:9–123:10. Plaintiffs offer that a POSA would have "an M.D., Ph.D., PharmD, or equivalent work experience in drug formulation, pharmacy, pharmacokinetics, or medicine." PFOF ¶ 77 n.7. Defendant proposes that "[a] POSA is a person who would have an advanced degree such as an M.D., Ph.D., PharmD, master's degree, or other advanced degree in an area related to chemistry, pharmaceutics, medicine or biology, with

and (4) objective indicia (secondary considerations) of nonobviousness, including commercial success, long-felt but unsolved need, failure of others, and other indicia. *See id.*

Defendant asserts that the Patent-in-Suit is invalid because it is obvious in view of prior art that would have motivated a POSA to arrive at the claimed dosing regimens with a reasonable expectation of success. Def. Br. at 18. Defendant further argues that secondary considerations do not overcome the prima facie case of obviousness. *Id*. at 44. Defendant also argues that a presumption of obviousness applies to the Patent-in-Suit, stating that the Representative Claims merely recite dosing and particle size ranges that overlap with ranges disclosed in the prior art. *Id.* at 9–12. The Court will address these arguments in turn.

To establish obviousness, Defendant primarily relied on three prior art references at trial: (1) a summary protocol for Janssen's PSY-3003 clinical study titled "A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Dose-Response Study to Evaluate the Efficacy and Safety of 3 Fixed Doses (50 Mg eq., 100 Mg eq., and 150 Mg eq.) of Paliperidone Palmitate in Subjects With Schizophrenia" (the "'548 Protocol"); (2) U.S. Patent No. 6,555,544 (the "'544 Patent"), a patent assigned to Plaintiff Janssen Pharmaceutica, N.V. titled "Aqueous Suspensions of Submicron 9-Hydroxyrisperidone Fatty Acid Esters"; and (3) International Patent Publication Number WO 2006/114384 (the "WO'384 Publication"), an international patent publication filed on behalf of Plaintiff Janssen Pharmaceutica, N.V. *See* PFOF ¶¶ 89, 93, 101; DFOF ¶¶ 138–39, 141, 178–80, 214; *see also* PTX-54, -55, -66; DTX-54, -55, -72.[11] Defendant also relies upon

several years of experience in the pertinent field and be capable of working in a team comprising others in the field or related fields." DFOF ¶ 136 (internal quotation marks omitted).

[11] The Court notes that the United States Patent and Trademark Office ("USPTO") considered a number of the prior art references at issue in this case and concluded that the Patent-in-Suit was not obvious in light of these references.

various other prior art references, which the Court will address throughout this Opinion where applicable.

In support of its obviousness arguments, Defendant proffered the following experts at trial: (1) Dr. Daniel Paul H. Wermeling, Pharm.D., FCCP, FASHP, Emeritus Professor at the University of Kentucky, College of Pharmacy,[12] and (2) Ivan T. Hofmann, Vice President and Managing Director of Gleason IP.[13] DFOF ¶¶ 14–16, 26–28; Final Pretrial Order at 41, 43–45.[14]

Plaintiffs contend that Defendant's obviousness arguments fail because a POSA would not have been motivated to create the claimed dosing regimens based on the prior art with a reasonable expectation of success. *See* Pls. Br. at 25–41. Plaintiffs further assert that secondary considerations support a finding of nonobviousness. *Id.* at 41–53. Plaintiffs also argue that no presumption of obviousness applies here, and that even if a presumption is applied, it has been rebutted. Pls. Br. at 54. In support of their arguments, Plaintiffs rely on the following experts: (1) Dr. Patrick J. Sinko, Ph.D., R.Ph, Distinguished Professor of Pharmaceutics in the Ernest Mario School of

[12] Dr. Wermeling is a named author on over 35 peer-reviewed publications related to pharmacokinetics, pharmacodynamics, and bioavailability. Final Pretrial Order at 42. He has also worked as a clinical investigator on studies related to pharmacokinetics and pharmacodynamics, and has received over 60 grants for such studies and is a named inventor on six U.S. patents, including two related to pharmaceutical compositions and methods of treatment using the pharmaceutical composition. *Id.*

[13] Mr. Hofmann's work experience includes litigation support and consulting engagements with a variety of pharmaceutical and biologics companies. Final Pretrial Order at 44. In his work in the pharmaceutical and life sciences industry, Mr. Hofmann has performed financial and economic analysis for hundreds of prescription pharmaceutical and biologic products, including virtually every major therapeutic class of drugs. *Id.*

[14] The Court will also consider the testimony of Dr. René S. Kahn, M.D., Ph.D., an expert who "testified . . . in the fields of psychiatry, psychotic disorders, and schizophrenia," to the extent he also opined on obviousness at trial. DFOF ¶ 9 (internal quotation marks omitted). Dr. Kahn is the Esther and Joseph Klingenstein Professor and System Chair of Psychiatry at the Icahn School of Medicine at Mount Sinai. Final Pretrial Order at 40. Dr. Kahn has conducted extensive research on schizophrenia and its treatment, has published over 900 research papers, and has been awarded multiple honors for his work in the field of psychiatry, including a Fulbright Scholarship. *Id.* at 40.

Pharmacy at Rutgers, The State University of New Jersey[15] (Trial Tr. at 1469:1–8; DFOF ¶ 42; Final Pretrial Order at 36–37); (2) Dr. Christian G. Kohler, M.D., Clinical Director of Neuropsychiatry in the Neuropsychiatry Division of the Department of Psychiatry at the Perelman School of Medicine of the University of Pennsylvania[16] (Trial Tr. at 1874:23–1875:6; DFOF ¶ 46; Final Pretrial Order at 37–38); and (3) Carla S. Mulhern, Managing Principal at Analysis Group[17] (Trial Tr. at 2576:24–2577:5; DFOF ¶ 49; Final Pretrial Order at 38–39). Plaintiffs also rely on the following fact witnesses: Dr. An Vermeulen, Dr. Srihari Gopal, and Dr. Mahesh Samtani. Final Pretrial Order at 29–31.

The Court has examined all asserted prior art references, both alone and in combination, as well as all expert testimony and secondary considerations to determine whether it would have been obvious to a POSA to arrive at the claimed dosing regimens. For the reasons discussed below, the Court finds that Defendant has failed to prove by clear and convincing evidence that the Patent-in-Suit is invalid based on obviousness pursuant to 35 U.S.C. § 103.

1. Scope of the Prior Art and Differences Between the Prior Art and the Claimed Invention

The Patent-in-Suit generally provides for a dosing regimen comprised of administering a 150 mg-eq. first loading dose of a sustained-release paliperidone palmitate formulation in the

[15] Dr. Sinko has over thirty years of research experience in drug formulation, drug delivery technology, and drug targeting. Final Pretrial Order at 36. Dr. Sinko has given approximately 169 lectures and published 175 articles, and serves as a grant reviewer for the National Institute of Health. *Id.* at 37.

[16] Dr. Kohler is the author of more than 80 peer reviewed research publications concerning neuropsychiatric disorders and their treatment, has over twenty years of teaching experience, and serves as a reviewer for a number of neuropsychiatry journals. Final Pretrial Order at 38.

[17] Ms. Mulhern has offered analyses of economic matters across a variety of industries, including pharmaceuticals, medical devices, automotive, computer hardware and software, consumer products, entertainment, semiconductors, and telecommunications over the course of her 25 years at Analysis Group. Final Pretrial Order at 39. Ms. Mulhern has been designated as a testifying expert in several forums, including federal and state courts, the International Trade Commission, the Patent Trial and Appeal Board, and various private arbitration tribunals. *Id.*

deltoid muscle on the first day of treatment, followed by a second loading dose of 100 mg-eq. in the deltoid muscle sometime during the sixth to tenth day of treatment, and then successive monthly (± 7 days) maintenance doses of 25 mg-eq. to about 150 mg-eq. in either the deltoid or gluteal muscle. *See generally* '906 Patent (DTX-1/PTX-1). The '906 Patent further provides for reduced loading and maintenance doses for renally impaired patients. *See id.* Therefore, to prove obviousness, Defendant must show by clear and convincing evidence that the claimed invention – which consists of a precise combination of dose amounts, dose timing, sites of administration, and particle size, designed for a patient in need of treatment for schizophrenia and other psychiatric disorders – would have been obvious to a POSA.

Defendant points to various scientific and patent publications that it contends render the claimed invention obvious.[18] The main prior art references focused on by the parties relate to the initiation of treatment with loading doses (the '548 Protocol), a specific formulation of paliperidone palmitate (the WO'384 Publication),[19] and monthly administration of aqueous

[18] In Teva's Proposed Findings of Fact and Conclusions of Law, it offers the following combinations of prior art references: (1) "Claim 2 is obvious in view of the '544 Patent and/or WO '384 in combination with the '548 Regimen, in view of Gibaldi, Goodman, Ereshefsky 1990, Ereshefsky 1993, Karagianis, Revill, and/or Janicak"; (2) "Claims 20 and 21 are obvious in view of the '544 Patent, WO'384, and '548 Regimen, in view of Gibaldi, Goodman, Ereshefsky 1990, Ereshefsky 1993, Karagianis, Revill, and/or Janicak"; (3) "Claims 10 and 13 are obvious in view of the '544 Patent, WO'384, and '548 Regimen, in view of Gibaldi, Goodman, Ereshefsky 1990, Ereshefsky 1993, Karagianis, Revill, Janicak, the '591 Application, Cleton 2007, and/or the 2006 Invega ER Label." DFOF ¶¶ 64–66. The Court has considered all of these prior art references, individually and in combination, insofar as they were presented at trial and in the parties' written submissions.

[19] The WO'384 Publication is an international patent publication filed by Janssen with the World Intellectual Property Organization describing a new process for creating raw paliperidone palmitate crystals, as opposed to a final paliperidone palmitate formulation such as the one utilized in the '906 Patent. DFOF ¶¶ 178, 203; PTX-66. The new method uses a "sterilization process replacing radiation with aseptic filters." Def. Br. at 22; *see also* DFOF ¶ 198. With respect to particle size, the WO'384 Publication states that the particles should have a "specific surface area>4m^2/g," meaning "that at least 90% of the particles have a diameter of less than 2,000 nm."

nanoparticle suspensions of paliperidone palmitate formulations to treat schizophrenia (the '544 Patent).[20] *See* Def. Br. at 18–26. Defendant asserts that, when considering these references and the other prior art in the record individually and in combination, a POSA would have been motivated to arrive at the claimed dosing regimens with a reasonable expectation of success. *See id.* at 18–43. Plaintiffs counter that the references on which Teva relies would not have motivated a POSA to create the claimed dosing regimens, that Teva's obviousness defense is based on impermissible hindsight, and that at least some of the references actually taught away from the claimed invention. *See* Pls. Br. at 25–41. Furthermore, Plaintiffs contend that any motivation to modify the prior art can only be found now with the benefit of non-public information, including Janssen's proprietary scientific data and the unpublished failures of Janssen's clinical trials. *See id.* at 29.

The Court will first address the '548 Protocol individually given that Teva's prior art combinations all involve modifying this prior art which discusses a dosing regimen for initiating treatment of paliperidone palmitate. *See* Pls. Br. at 29; Def. Br. at 23. The Court will then discuss all of the prior art in connection with a POSA's motivation to arrive at the specific claims. As explained below, Teva has failed to show that a POSA would have been motivated to arrive at the

DFOF ¶ 200; PTX-66 cols. 5:23–25, 7:25–26. The publication also instructs that particle size can be altered through a milling process. DFOF ¶¶ 201–202.

[20] The '544 Patent teaches how to make a sustained-release paliperidone palmitate formulation that is therapeutically effective for at least three weeks, but does not teach the use of loading doses or other key features of the '906 Patent such as uniform dosing or particularized injection sites. DFOF ¶ 145; PFOF ¶¶ 94–97; PTX-55. The '544 Patent describes four different formulations of paliperidone palmitate with varying particle sizes and pertinent characteristics, and teaches intramuscular injection of the formulation every three weeks at a dosage range from about 2 to 4 mg/kg of body weight. DFOF ¶¶ 156, 167, 174; PTX-55.

claimed dosing regimens with a reasonable expectation of success based on any of the prior art, considered alone or in combination, discussed at trial.[21]

2. The Prior Art Would Not Have Motivated a POSA to Arrive at the Dosing Regimens Claimed in the '906 Patent

a) The '548 Protocol

The '548 Protocol is a published two-page summary protocol of Janssen's unsuccessful PSY-3003 clinical trial aimed at measuring the safety and efficacy of administering "fixed doses" of either 50, 100, or 150 mg-eq. of paliperidone palmitate "in the gluteal muscle" for "treating subjects with schizophrenia." DTX-55 at 1; *see also* DFOF ¶ 557.[22] In the study, equal doses were to be administered on "Days 1, 8, 36, and 64." DTX-55 at 1; *see also* DFOF ¶ 557. The "hypothesis" of the study was "that the 3 fixed doses of paliperidone are each more efficacious than placebo in treating subjects with schizophrenia." DTX-55 at 1; *see also* PFOF ¶ 91.[23] Janssen received the PSY-3003 results in August 2006. PFOF ¶ 35. The results indicated that PSY-3003 "failed to demonstrate superiority of any dose of [paliperidone palmitate] as compared to placebo

[21] The Court notes that the parties presented very little testimony and evidence on the Janicak and Revill prior art references at trial and only refer to these references in passing in their briefing. Nonetheless, the Court has considered these references in its obviousness analysis and finds that they do not render the claimed invention obvious based on their discussion of oral paliperidone and other meaningful differences. *See* PFOF ¶¶ 118–19; DFOF ¶¶ 232–33, 264–67.

[22] Plaintiffs argue that Defendant failed to establish that the '548 Protocol qualifies as prior art because it was printed on March 8, 2018, from a frequently-updated Internet database and does not indicate which portions were publicly available in 2007. *See* PFOF ¶ 90. This argument is unpersuasive. A cursory review of the versions of the '548 Protocol in the record indicate that the document was "[u]pdated" on September 20, 2005, and show the "[v]iew . . . on" September 20, 2005. PTX-54 at 1; DTX-55 at 1. The Court will therefore consider the '548 Protocol in its entirety.

[23] Over the course of the PSY-3003 study, a "medical kit allocation error" caused some subjects assigned to the placebo treatment group to receive 150 mg-eq. doses and some subjects assigned to the 150 mg-eq. treatment group to receive the placebo. DFOF ¶ 559. As a result, only thirty subjects consistently received the four intended 150 mg-eq. doses during the study. *Id.*; *see also* Trial Tr. (Gopal) at 1063:23–1064:8. At trial, however, Dr. Vermeulen acknowledged that the error "had nothing to do with the 150-milligram dose regimen itself" and "was just an error in the way the study was conducted[.]" DFOF ¶ 560 (internal citations and quotation marks omitted).

in the United States," "failed to show superiority of the 50 and 150 mg-eq. doses world-wide," and showed that the 100 mg-eq. dose—the only dose to establish statistical efficacy—was not fast-acting, first demonstrating superiority on Day 36. *Id.* ¶ 35; *see also* DFOF ¶ 558.

The parties agree that the '548 Protocol does not contain clinical results or safety data, and that a POSA would have to look beyond this reference in order to understand how the '548 Protocol worked in subjects. Pls. Br. at 30–31; Def. Br. at 25. At trial, Dr. Wermeling, Defendant's obviousness expert, explicitly acknowledged that the '548 Protocol "is a protocol without any results" and "does not provide any safety or efficacy data." Trial Tr. (Wermeling) at 423:20–21, 471:10–14.

The '548 Protocol and the '906 Patent differ in several material respects. The '548 Protocol discloses **equal** doses of paliperidone palmitate administered in the **gluteal** muscle on fixed treatment days, while the '906 Patent contains regimens comprised of **unequal** doses (Claim 2), two of which must be administered in the **deltoid** muscle (Claims 2 and 10), and a broader dosing window for the second and monthly maintenance doses (Claims 2 and 10). Defendant asserts that the '548 Protocol provides a proper starting point for arriving at the claimed dosing regimens because it "provided guidance on using loading doses followed by monthly administration of paliperidone palmitate." Def. Br. at 23, 26. But Defendant fails to adequately explain why a POSA would modify the '548 Protocol's teachings in the precise ways required to achieve the dosing regimens claimed in the '906 Patent, and the mere fact that the '548 Protocol and the '906 Patent contain some similar features is not enough to show obviousness. *See Belden Inc. v. Berk-Tek LLC*, 805 F.3d 1064, 1073 (Fed. Cir. 2015) (noting that "obviousness concerns whether a skilled artisan not only *could have made* but *would have been motivated to make* the combinations or modifications of prior art to arrive at the claimed invention"); *Heidelberger Druckmaschinen AG*

v. Hantscho Commercial Prods., Inc., 21 F.3d 1068, 1072 (Fed. Cir. 1994) ("When the patented invention is made by combining known components to achieve a new system, the prior art must provide a suggestion or motivation to make such a combination.").

One issue with starting from the '548 Protocol is that it contains no information about the safety of the dosing regimen or its efficacy (the study was actually ineffective as discussed above), and Defendant has failed to persuasively argue, among other things, how a POSA would know to alter the equal doses in the gluteal muscle described in the '548 Protocol to arrive at the unequal loading doses in the deltoid claimed by the '906 Patent without knowing the results of the trial. As Dr. Sinko credibly testified, without such safety and efficacy information, a POSA would have had no reason to alter the regimen disclosed in the reference. *See* Trial Tr. (Sinko) at 1580:2–16 ("[T]here's no safety data available or efficacy data available that would give the motivation to make any changes. . . . And so there would be no motivation for a person of skill to consider [adopting unequal loading doses to initiate treatment] because once again, there's no data to support that change.").[24] In fact, the only way to know how to modify the '548 Protocol to match the '906 Patent would be to look back at the protocol later with its results in hand, but that type of hindsight analysis is impermissible here.[25]

[24] Janssen also asserts that Teva presents an internally inconsistent argument by claiming "that a person skilled in the art would have selected the dosing regimens of the 548 Protocol in order to avoid oral supplementation, reach therapeutic plasma levels faster, and reduce the risk of relapse," and simultaneously contending "that these same motivations would have led one to modify the 548 Protocol dosing regimens to arrive at the claimed inventions." Pls. Reply Br. at 17 (internal citations and quotation marks omitted). While the Court acknowledges that there may be some inconsistency in Teva's argument, it nevertheless examines the substance of Teva's arguments on this matter.

[25] Dr. Wermeling also appeared to rely on impermissible hindsight in forming his obviousness opinion. As the Federal Circuit has made clear, "[o]bviousness 'cannot be based on the hindsight combination of components selectively culled from the prior art to fit the parameters of the patented invention.'" *Cheese Sys., Inc. v. Tetra Pak Cheese & Powder Sys., Inc.*, 725 F.3d 1341, 1352 (Fed. Cir. 2013) (quoting *ATD Corp. v. Lydall, Inc.*, 159 F.3d 534, 546 (Fed. Cir. 1998)).

At trial, Dr. Wermeling asserted that motivation to modify the '548 Protocol to align with the dosing regimen of the '906 Patent can be derived from Ereshefsky's teachings about high loading doses and a desire to use LAIs to treat "acute life-threatening circumstances." Trial Tr. (Wermeling) at 321:13–14, 372:15–24, 475:10–17. As discussed in more depth below, Ereshefsky did not discuss paliperidone palmitate, uniform dosing, or unequal loading doses, all of which are present in and integral to the '906 Patent. Moreover, Dr. Wermeling's assertion about the use of LAIs in acute life-threating circumstances was contradicted by the testimony of Dr. Kahn, Defendant's other technical expert. According to Dr. Kahn, "long-acting injectables are not designed to be used in emergency situations" because "[t]hey don't work fast enough." Trial Tr. (Kahn) at 90:12–19. This inconsistency between the experts' testimony belies Defendant's theory of motivation, and Defendant has not carried its burden to establish motivation to modify the '548 Protocol by clear and convincing evidence. *See Heidelberger Druckmaschinen*, 21 F.3d at 1072.[26]

During his deposition, Dr. Wermeling conceded that he "formed [his] opinions on obviousness" by "look[ing] at the '906 Patent claims first" and then "went back to see if [he] could find the elements that are in the '906 Patent claims in these other references next." Trial Tr. (Wermeling) at 359:21–360:15. Although he attempted to disavow this testimony at trial on the basis that it was "not particularly accurate" and did not "fully accurately describe" his "process," he elsewhere admitted that his "memory from a year ago is going to be better than a year later." *Id.* at 357:12–25, 358:14–359:5, 359:21–360:15. Dr. Wermeling's testimony also contained inconsistencies regarding his views on "routine optimization." *See, e.g.*, Trial Tr. (Wermeling) at 361:25–364:24. Thus, considering Dr. Wermeling's testimony in its entirety, the Court finds that Dr. Wermeling's deposition admissions undermine his obviousness opinion and that Dr. Wermeling's testimony has credibility issues.

[26] Plaintiffs further contend that the claimed invention is not obvious because it solved a problem that was not known in the prior art. Pls. Br. at 34–35. Specifically, they argue that because the '548 Protocol study was designed to achieve rapid and sustained efficacy, and because the prior art did not disclose the unexpected failures of the study, a POSA would have had no reason to solve the problems with the '548 Protocol's equal dose regimen. *Id.* "[W]here a problem was not known in the art, the solution to that problem may not be obvious, because ordinary artisans would not have thought to try at all because they would not have recognized the problem." *Forest Lab'ys, LLC v. Sigmapharm Lab'ys, LLC*, 918 F.3d 928, 935 (Fed. Cir. 2019) (internal citation and quotation marks omitted). As Dr. Wermeling conceded, the '548 Protocol does not contain any results or data on safety or efficacy. Trial Tr. (Wermeling) at 423:20–21, 471:10–14. Indeed, as

The '548 Protocol is a failed study conducted by Janssen that examined using paliperidone palmitate to treat schizophrenia. Yet, for the reasons stated above, even starting from this protocol, Teva has failed to show that a POSA would be motivated to modify the '548 Protocol to comport with the '906 Patent without utilizing safety/efficacy information that was unavailable or impermissible hindsight. The Court will next further analyze Teva's motivation to modify the prior art, including the '548 Protocol, with respect to each claim.

b) Claim 2 – Primary Dosing Regimen

Claim 2 provides for a dosing regimen of high, unequal loading doses in the deltoid muscle followed by monthly maintenance doses in the deltoid or gluteal muscle. PFOF ¶ 7. Specifically, the claim instructs administering 150 mg-eq. of a sustained-release paliperidone palmitate formulation in the deltoid muscle on the first day of treatment, followed by administering 100 mg-eq. in the deltoid muscle six to ten days later, and then successive monthly (±7 days) maintenance doses of 25 to 150 mg-eq. in either the gluteal or deltoid muscle. '906 Patent (DTX-1/PTX-1). Defendant argues that a POSA would have been motivated to arrive at Claim 2 in view of the prior art. *See* Def. Br. at 26–28. After careful consideration of the entire record, the Court is not persuaded.

i. Claim 2 – Deltoid Administration

A key component of Claim 2 is the requirement that the first and second loading doses are given in the deltoid muscle. '906 Patent (DTX-1/PTX-1) col. 32:15–24. Contrary to Defendant's assertions, the prior art would not have motivated a POSA to initiate treatment with deltoid injections as is instructed in the '906 Patent. Indeed, as Dr. Wermeling conceded at trial, none of

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discussed above, Janssen only discovered a solution to the study's problems after conducting additional internal studies and reviewing internal data. Therefore, a POSA would not have recognized the problems associated with the '548 Protocol regimen, and this fact further supports a finding of nonobviousness.

the three primary prior art references—the '548 Protocol, the '544 Patent, or the WO'384 Publication (discussed above)—teach deltoid administration of loading doses. *See* Trial Tr. (Wermeling) at 477:16–25 (Dr. Wermeling testified that he "would have [his] own reasoning as a POSA to understand that's an option."), 504:25–505:8, 512:20–24. As explained above, the '548 Protocol involved gluteal injections, not deltoid injections. DTX-55 at 1. Additionally, as Dr. Wermeling admitted, the WO'384 Publication would not "point you in the direction of giving a Day 1 dose and a second dose on Day 6 to 10 in the deltoid specifically." Trial Tr. (Wermeling) at 512:20–24. As to the '544 Patent, the testing described therein involved an "injection . . . given in the biceps femoris of the left hind paw" of "a beagle dog," not deltoid administration in humans. Trial Tr. (Wermeling) at 504:25–505:8; *see also* Trial Tr. (Sinko) at 1533:19–22 (noting that the '544 Patent does not "provide any guidance on a preferred injection site for a human"). While Dr. Wermeling opined that a POSA knew "you could use various [injection] sites" for dosing, such as the deltoid, gluteus, and vastus lateralis, he conceded that selecting the deltoid was only "an option" and that "[o]ther options would have been reasonable too." Trial Tr. (Wermeling) at 323:4–11, 476:19–23. As explained above, however, the obviousness inquiry "concerns whether a skilled artisan not only *could have made* but *would have been motivated to make* the combinations or modifications of prior art to arrive at the claimed invention." *See Belden Inc.*, 805 F.3d at 1073; *see also InTouch Techs., Inc. v. VGO Commc'ns, Inc.*, 751 F.3d 1327, 1352 (Fed. Cir. 2014).

Defendant also argues that two textbooks—(1) "Goodman & Gilman's The Pharmacological Basis of Therapeutics" ("Goodman"); and (2) "Gibaldi's Drug Delivery Systems in Pharmaceutical Care" ("Gibaldi")—would motivate a POSA to arrive at the claimed regimens because they teach that deltoid injections lead to faster absorption than gluteal injections. Def. Br.

at 20; DFOF ¶¶ 223, 225, 227; PTX-64, -65; DTX-91, -93.[27] A holistic review of these references indicates, however, that neither discloses deltoid administration of LAI loading doses. Indeed, while Dr. Wermeling relied on a passage from Goodman stating that "[g]enerally, the rate of absorption following injection of an aqueous preparation into the deltoid or vastus lateralis is faster than when the injection is made into the gluteus maximus," Goodman goes on to note that "[s]low, constant absorption from the intramuscular site results if the drug is . . . suspended in various other repository (*depot*) vehicles." Trial Tr. (Wermeling) at 323:2–324:23, DDX3-84, DTX-93 at 32; *see also* PTX-65 at 8 (characterizing absorption rate of drug suspended in repository vehicle as "[v]ery slow"). As Dr. Sinko persuasively conveyed through his testimony, Goodman suggests that in the context of drug suspensions, such as the "aqueous particle nanosuspensions" or "depot formulation" claimed in the '906 Patent, "the formulation," rather than the injection site, "would be controlling the rate of absorption." Trial Tr. (Sinko) at 1533:23–1536:21. Thus, the Court finds that Goodman would not motivate a POSA to use deltoid injections for the claimed formulation.

Similarly, the Court finds that the Gibaldi reference would not have motivated a POSA to initiate treatment with deltoid injections as claimed in the '906 Patent. In support of its position, Defendant cites to Gibaldi's teachings that "[t]he [intramuscular] injection site is usually the deltoid muscle . . . or the vastus lateralis muscle," that the absorption rate "of drugs depend[s] on biopharmaceutical factors such as formulation characteristics and the physiology of the injection site," that deltoid injections "are absorbed faster than gluteal injections . . . likely due to the increased blood flow in the deltoid muscle . . .," and that "[intramuscular] injections are available in immediate-release formulations as well as depot formulations for sustained release." DTX-91

[27] As Defendant notes, although the parties presented two different editions of Goodman (*see* PTX-65, DTX-93), "the teachings relied on are the same in both." DFOF ¶ 226.

at 4–5; DFOF ¶¶ 221, 223–25. Defendant's argument fails to adequately address, however, that Gibaldi also teaches that depot injections are not indicated for treatment initiation, as claimed in the '906 Patent. Indeed, as Gibaldi expressly states, "[d]epot injections release the drug slowly" and "are long-acting dosage formulations indicated for maintenance treatment rather than initiation of therapy." DTX-91 at 5; *see also* PTX-64 at 38 (explaining that "[i]n the acute phase of schizophrenia, short-acting injections may be required because of their quick action," while "[i]n the maintenance phase of therapy for schizophrenia, administration of an atypical agent in a long-acting or depot dosage formulation may be desirable"). When Dr. Wermeling was questioned about this teaching on cross-examination, he admitted that Gibaldi "says that [about depot injections], but that's not my usage of Gibaldi." Trial Tr. (Wermeling) at 472:2–9. In other words, Dr. Wermeling's testimony suggests that he selectively relied on only some of Gibaldi's teachings in forming his opinion rather than the reference as a whole. The Federal Circuit has made clear, however, that the prior art "must be considered in its entirety, i.e., as a *whole*, including portions that would lead away from the invention in suit." *Panduit Corp. v. Dennison Mfg. Co.*, 810 F.2d 1561, 1568 (Fed. Cir. 1987). Thus, when viewed as a whole, the Court cannot say that Gibaldi would motivate a POSA to initiate treatment using deltoid injections as directed in Claim 2.

Finally, Defendant contends that patient preference would have motivated a POSA to use deltoid administration. *See* Def. Br. at 20–21. This argument is not fully supported by the record. For example, as Dr. Gopal explained, the participants in the PSY-3007 study were divided "about half and half" between choosing deltoid and gluteal injections. Trial Tr. (Gopal) at 1180:20–1181:2 (explaining that "in the United States, the patients tend to prefer getting the injections in the arm because you don't have to pull down your pants and stigmatize yourself; whereas in other countries, like in Asia, they tend to be lighter, so they prefer getting the injection in the gluteal").

In addition, Gibaldi generally suggests administering depots in the gluteal muscle over the deltoid muscle "because [a deltoid injection] causes discomfort and pain at the injection site." DTX-91 at 15. Moreover, as Plaintiffs correctly note, even if some patients prefer deltoid injections, such preferences would suggest at most using deltoid administration on an individualized basis. Pls. Reply at 20. The '906 Patent, however, claims a generalized dosing regimen. In essence, Defendant's argument is that "a POSA would not have been dissuaded from deltoid injections," (Def. Br. at 26), but this assertion does not satisfy Defendant's burden. *See Endo Pharm. Sols., Inc. v. Custopharm Inc.*, 894 F.3d 1374, 1380 (Fed. Cir. 2018) ("To meet its burden, Custopharm needed to do more than merely show that the prior art does not preclude lowering the dose of TU."). Accordingly, the Court finds that Defendant has not established motivation to use deltoid injections by clear and convincing evidence.

ii. *Claim 2 – Unequal Loading Doses*

A second key feature of Claim 2 is the use of unequal loading doses. '906 Patent (DTX-1/PTX-1) col. 32:15–24. The Court also finds that Defendant has not met its burden of showing that a POSA would have been motivated to use unequal loading doses as claimed in the '906 Patent. According to Defendant, two articles by Dr. Larry Ereshefsky et al.—a 1990 article titled "Kinetics and Clinical Evaluation of Haloperidol Decanoate Loading Dose Regimen" ("Ereshefsky 1990") and a 1993 article titled "A Loading-Dose Strategy for Converting From Oral to Depot Haloperidol" ("Ereshefsky 1993")—and a 2001 article by Dr. James L. Karagianis et al. titled "Rapid Tranquilization With Olanzapine in Acute Psychosis: A Case Series" ("Karagianis") render the claimed regimens obvious. *See* Def. Br. at 24–25, 27, 29; DTX-88, -89, -96.

Defendant's argument fails for three reasons.[28] First, as their titles suggest, neither the Ereshefsky nor Karagianis references concern paliperidone palmitate; the Ereshefsky references involve haloperidol decanoate dosing, and Karagianis relates to oral olanzapine. Trial Tr. (Wermeling) at 312:17–313:20; DTX-88, -89, -96. As Dr. Sinko explained, because these references concern "different drugs and different formulations" than paliperidone palmitate, their "pharmacokinetics and how they act are . . . different." Trial Tr. (Sinko) at 1566:18–1567:5. Defendant's expert Dr. Wermeling agreed with this opinion. *See* Trial Tr. (Wermeling) at 513:17–24 (agreeing that "haloperidol decanoate and paliperidone palmitate have different PK or pharmacokinetic profiles"). Thus, a POSA would know that "you really can't correlate" their teachings to "an injectable version of paliperidone palmitate." Trial Tr. (Sinko) at 1566:18–1567:11.

Second, unlike the '906 Patent, the Ereshefsky and Karagianis references teach individualized, rather than generalized, dosing. Indeed, as Dr. Wermeling acknowledged at trial, Ereshefsky 1990 involved dosing patients "on an individual basis" (Trial Tr. (Wermeling) at 517:10–518:6), and Dr. Sinko similarly testified that Ereshefsky taught "patient-specific approaches" (Trial Tr. (Sinko) at 1569:18–1570:1, 1573:19–1574:13). Furthermore, Karagianis states that the patients in the case series were "not dosed according to a protocol-dosing regimen." DTX-96 at 4; *see also* Trial Tr. (Sinko) at 1577:4–12 (noting that patients in Karagianis received "a personalized dose"). This distinction between dosing approaches undercuts Defendant's argument that Ereshefsky and Karagianis would lead a POSA to the claimed dosing regimens.

[28] Defendant also cites Karagianis's teaching on "rapid neuroleptization," which Defendant characterizes as an "older loading dose strategy" involving very high doses of oral or short-acting injectables, to argue that Karagianis suggests using a high-loading dose strategy. DFOF ¶¶ 258–62; Trial Tr. (Kahn) at 2383:18–2384:11. This argument is unavailing. As Defendant's own expert Dr. Kahn explained, rapid neuroleptization "has nothing to do with the use of long-acting injectables" and treatment providers "don't do this anymore." Trial Tr. (Kahn) at 2382:8–2384:11.

Lastly, these references do not disclose unequal loading doses as claimed in the '906 Patent. Specifically, Defendant contends that Ereshefsky 1993 taught initiating therapy with unequal dose amounts. *See* Def. Br. at 27. While Ereshefsky 1993 does note that the loading dose was "administer[ed] . . . in two or more sequential injections" of "consecutive divided doses" for safety reasons, the reference does not teach the use of unequal loading dose amounts. DTX-89 at 4. To the contrary, it provides that patients received initial "consecutive divided doses of 100 to 200 mg every three to seven days until the full amount is given," and the haloperidol decanoate doses were not reduced until "the second and third months." *Id.*; Trial Tr. (Wermeling) at 322:17–323:1. Ereshefsky 1990 contains similar teachings. *See* DTX-88 at 3, 5–7 (citing case studies and disclosing initial "consecutive divided doses . . . until the full amount was administered").[29] Claim 2 of the '906 Patent, by contrast, directs two loading doses of unequal amounts of paliperidone palmitate. '906 Patent (DTX-1/PTX-1). Accordingly, the Court finds that a POSA would not have been motivated to create the Claim 2 dosing regimen in view of the prior art.

c) Claims 10 and 13 – Renal Impairment Claims

Claims 10 and 13 set forth dosing regimens for patients with renal impairment. Under these claims, renally impaired patients receive reduced loading doses of from about 75 mg-eq. of paliperidone palmitate in the deltoid muscle on both the first day of treatment and sixth to about tenth day of treatment, followed by successive monthly maintenance doses (± 7 days) of about 25 mg-eq. to about 75 mg-eq. in either the deltoid or gluteal muscle. *See* '906 Patent (DTX-1/PTX-1). According to Defendant, Claims 10 and 13 are obvious because several prior art references taught reduced doses for renal impairment. *See* Def. Br. at 36–38. The Court disagrees.

[29] Ereshefsky 1990 also notes that certain patients did not actually "receive a true loading dose" because those doses were "not given as a single injection." DTX-88 at 7.

First, the references on which Dr. Wermeling relied would not have motivated a POSA to achieve the claimed regimens. At trial, Dr. Wermeling testified that, in addition to the three primary prior art references (the '548 Protocol, the '544 Patent, and the WO'384 Publication), a combination of three other references teach "a 50 percent dose reduction from the maximum dose for patients with mild renal impairment." Trial Tr. (Wermeling) at 332:25–333:12; *see also* DFOF ¶ 375. The three additional references are a clinical trial abstract titled "PII-46[:] Effects of Renal Impairment on the Pharmacokinetic Profile of Paliperidone Extended-Release Tablets" (referred to by the parties as "Cleton 2007"), the Invega (paliperidone) Extended Release Tablets label (the "Invega ER Label"), and U.S. Patent Application No. 2007/0197591 (the "'591 Application"). Dr. Wermeling opined that based upon these three prior art references, "it would have been reasonable to do the 50 percent reduction for the loading dose strategy." Trial Tr. (Wermeling) at 333:9–12. Dr. Wermeling's conclusions, however, are unsupported by the record.

Cleton 2007 concerned orally administered paliperidone, rather than the LAI paliperidone palmitate at issue here. PTX-56; DTX-84; Trial Tr. (Sinko) at 1586:11–15; Trial Tr. (Wermeling) at 530:15–531:18 (admitting that Cleton 2007 is not "talking about an injectable paliperidone palmitate"). In addition, while Dr. Wermeling testified that Cleton 2007 teaches that "the two measures of exposure . . . the maximum concentration, . . . and the total exposure by AUC, as area under the curve, is basically doubling for patients who have renal impairment" and "would be a strong consideration for reducing the dose" in a renally impaired patient (Trial Tr. (Wermeling) at 330:19–331:9), his conclusion ignored that Cleton 2007 only suggests dose reductions for patients with moderate and severe renal impairment. Indeed, contrary to Dr. Wermeling's assertions, Cleton 2007 did not suggest a reduction in dosing for patients with mild renal impairment. PTX-56; DTX-84; Trial Tr. (Sinko) at 1586:12–1587:8 (explaining that Cleton 2007 suggests "no dose

reduction for mild renal impairment"). In contrast, the '906 Patent "focuses on mild renal impairment." Pls. Br. at 70.

Defendant's reliance on the Invega ER Label is similarly unavailing. Like Cleton 2007, the Invega ER Label concerns oral paliperidone, not injectable paliperidone palmitate. PTX-57; DTX-102; Trial Tr. (Wermeling) at 531:15–18. Additionally, while Defendant argues that the Invega ER Label can be read to suggest a 50 percent reduction from the **maximum** recommended dose for patients with normal renal function to the **maximum** recommended dose for patients with mild renal impairment (with Janssen challenging that suggestion), a POSA developing a dosing regimen would not start from the maximum recommended dose, but instead would start with the general recommended dose for patients with normal renal function. *See* Trial Tr. (Sinko) at 1587:20–22 ("[I]t's actually more appropriate to start with the recommended dose in healthy patients."); PTX-57 at 26; DTX-102 at 26. Furthermore, as Dr. Sinko convincingly testified, the label does not teach "just a straight 50 percent" reduction for dosing patients with renal impairment as it provides a range of maximum recommended doses that are dependent on a patient's level of renal impairment. Trial Tr. (Sinko) at 1587:20–1588:6.

Defendant further argues that the '591 Application teaches that doses must be reduced for patients with renal impairment. *See* Def. Br. at 37. As Defendant concedes, however, the '591 Application "is directed to . . . patients with hepatic (or liver) impairment," not renal impairment. *Id.* at 36; PTX-69; DTX-108. Moreover, while Defendant contends that the '591 Application teaches that paliperidone is excreted through the kidneys, this purported teaching does not, alone or in combination with Cleton 2007 as Defendant suggests, render the claimed regimens obvious. *See* Def. Br. at 36–37; DFOF ¶ 272. As explained above, the dosing regimens address patients with mild renal impairment, and neither the '591 Application nor Cleton 2007 expressly teach LAI

paliperidone palmitate dose reductions for mild renal impairment. *See* PTX-69; DTX-108; Trial Tr. (Sinko) at 1586:12–1587:8. Therefore, the Court finds that Cleton 2007, the Invega ER Label, and the '591 Application, whether considered individually or in combination, would not motivate a POSA to arrive at the claimed dosing regimens for patients with mild renal impairment.

Finally, even if the Court were to find that the prior art teaches a 50 percent dose reduction for patients with mild renal impairment, this teaching would not actually lead to the claimed invention. Indeed, if the 150/100 mg-eq. loading doses of Claim 2 were reduced by half, the regimen would consist of 75/50 mg-eq. loading doses, not 75/75 mg-eq. as claimed in the Patent-in-Suit. Thus, applying a 50 percent reduction would not yield the regimens disclosed in Claims 10 and 13.

d) Claims 20 and 21 – Paliperidone Palmitate Properties

Claims 20 and 21 recite the properties of the paliperidone palmitate formulation used in the claimed dosing regimens. *See* '906 Patent (DTX-1/PTX-1) col. 34:32–51. Specifically, these claims direct, among other things, that the sustained release depot formulation "is an aqueous nanoparticle suspension consist[ing] essentially of . . . paliperidone palmitate having an average particle size (d50) of from about 1600 nm to about 900 nm." *Id.* d50 refers to a distribution of particle size which indicates that 50 percent of the particles are below the reported size. DFOF ¶ 625. Defendant contends that a POSA would have been motivated to select the claimed particle sizes in view of the prior art. The Court is not persuaded.

Both parties' obviousness experts testified that particle size affects dosing strategy. *See, e.g.*, Trial Tr. (Wermeling) at 291:12–19 (noting that "the pharmacokinetic properties of such a formulation are derived from the formulation itself" and "if you wanted to impart changes in the pharmacokinetics, you could change the particle size"); Trial Tr. (Sinko) at 1544:1–6 (explaining

that particle size "controls the rate of dissolution, release and, ultimately, absorption for a formula like this"). Of the three primary prior art references—the '548 Protocol, the '544 Patent, and the WO'384 Publication—only the '548 Protocol discloses a treatment initiation regimen for paliperidone palmitate. *See* DTX-55. This reference, however, neither specifies the characteristics of the formulation used in the study, nor any information about the formulation's particle size. *See id.* Furthermore, while the two other primary art references discuss particle size for paliperidone palmitate formulations, they do not suggest that that these formulations are appropriate for a treatment initiation regimen. *See* DTX-54; DTX-72; Trial Tr. (Sinko) at 1538:2–1539:6, 1543:9–13, 1550:18–24, 2256:12–14; Trial Tr. (Wermeling) at 506:24–507:1, 511:15–512:8.

With respect to the '544 Patent, it describes four different paliperidone palmitate formulations, referred to as Formulations A, B, C, and D. DTX-54 cols. 8–9; Trial Tr. (Wermeling) at 483:3–11. The d50 particle sizes for the formulations reported in the '544 Patent are: (1) "Formulation A," d50 of 6030 nm; (2) "Formulation B," d50 of 1380 nm; (3) "Formulation C," d50 of 740 nm; and (4) "Formulation D," d50 of 520 nm. DTX-54 col. 9:25–31; Trial Tr. (Wermeling) at 486:23–487:11. Thus, only Formulation B has a d50 particle size that falls within the particle size limitations recited in the '906 Patent, which requires "an average particle size (d50) of from about 1600 nm to about 900 nm." '906 Patent (DTX-1/PTX-1) col. 34:32–51; Trial Tr. (Sinko) at 1530:15–1531:1.

A problem with Formulation B—the only formulation with a proper d50 particle size as claimed in the '906 Patent—is that the '544 Patent expressly teaches away from using this formulation based on its effective particle size limitations, which require that the formulation has a d90 particle size of "less than 2000 nanometers." DTX-54 cols. 3:42–44, 5:16–21, 9:25–31, 10:27–29. d90 is another form of measurement and refers to a distribution of particle size which

indicates that 90 percent of the particles are below the reported size. DFOF ¶ 625. Formulation B has a d90 particle size of 6830 nm, which is significantly above 2000 nm. DTX-54 col. 9:25–31. Consequently, as Dr. Sinko credibly opined, a POSA considering the '544 Patent would have been dissuaded from selecting Formulation B. *See* Trial Tr. (Sinko) at 1783:4–1785:1 (testifying that a POSA would "eliminate . . . [Formulation] B" from further consideration based on "the two critical parameters, the particle size and the specific surface area" taught in the '544 Patent).[30] Thus, because the prior art "must be considered in its entirety, i.e., as a *whole*, including portions that would lead away from the invention in suit," the Court finds that the '544 Patent would not motivate a POSA to arrive at the claimed particle size. *Panduit Corp.*, 810 F.2d at 1568.

Defendant argues that Formulation C, having a d50 of 740 nm, would also motivate a POSA to select the claimed particle size ranges. *See* Def. Br. at 34. This argument is unpersuasive. As Plaintiffs correctly note, Dr. Wermeling's opinion that Formulation C's d50 particle size of 740 nm is covered by the '906 Patent is contradicted by Defendant's own assertion in its proposed findings of fact that a "d50 of 600–800 nm" is "outside the claimed range." Pls. Reply Br. at 22; *compare* Trial Tr. (Wermeling) at 494:16–22 (testifying that he "would consider 740 [to be] in the range" of the claimed "about 900 nanometers" d50 particle size), *with* DFOF ¶ 527 (arguing that the [redacted]).

Finally, Defendant's argument that the WO'384 Publication, in combination with the '544 Patent, would motivate a POSA to arrive at Claims 20 and 21 is unavailing. *See* Def. Br. at 34–36.

[30] Formulations C and D were also "the only formulations that were tested for stability." Trial Tr. (Wermeling) at 491:14–22; DTX-54 col. 9:33–35. As Dr. Sinko explained, a POSA would have understood that the selection of Formulations C and D for stability testing suggests that they "had the most promising attributes that you want to study further." Trial Tr. (Sinko) at 1529:24–1530:8.

By Defendant's own concession, the WO'384 Publication "made no new disclosure on particle size," and a POSA would refer back to the '544 Patent's teachings on particle size. *Id.* at 23, 34–36; *see also* DTX-72. Indeed, Dr. Wermeling agreed at trial that the WO'384 Publication discussed measurements of raw materials before milling, and "none of [the 32 measurements for particle size described in the WO'384 Publication] have a d50 of between about 1600 and 900 nanometers." Trial Tr. (Wermeling) at 511:10–14. Dr. Wermeling further agreed that the WO'384 Publication teaches that "what you want is an average particle size d90 of less than 2000 nanometers corresponding to a specific surface area greater than 4 meters squared per gram"—the same teaching as the '544 Patent. *Id.* at 560:24–561:5; DTX-72 at 6. Thus, the WO'384 Publication does not alter the Court's analysis, and Defendant has failed to show that a POSA would have been motivated to select the claimed particle size.

3. A POSA Would Not Have a Reasonable Expectation of Success in Arriving at the Claimed Dosing Regimens

In addition to motivation, "[a]n obviousness determination requires that a skilled artisan would have perceived a reasonable expectation of success in making the invention in light of the prior art." *Amgen Inc. v. F. Hoffman-La Roche Ltd*, 580 F.3d 1340, 1362 (Fed. Cir. 2009); *see also Procter & Gamble Co. v. Teva Pharm. USA, Inc.*, 566 F.3d 989, 994 (Fed. Cir. 2009) ("A party seeking to invalidate a patent based on obviousness must demonstrate 'by clear and convincing evidence that a skilled artisan would have been motivated to combine the teachings of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success in doing so.'") (quoting *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1361 (Fed. Cir. 2007). The Federal Circuit has noted that "[t]he presence or absence of a reasonable expectation of success is . . . a question of fact." *Novartis Pharm. Corp. v. W.-Ward*

Pharm. Int'l Ltd., 923 F.3d 1051, 1059 (Fed. Cir. 2019) (internal citation and quotation marks omitted). The Court finds that Defendant has not met its burden for several reasons.

First, the unpredictability of developing treatment initiation regimens using LAIs supports a finding of nonobviousness. The Federal Circuit has noted that "evidence showing unpredictability in the art" suggests "that one of ordinary skill would not have been motivated to combine the references with a reasonable expectation of success." *Honeywell Int'l Inc. v. Mexichem Amanco Holding S.A. DE C.V.*, 865 F.3d 1348, 1354 (Fed. Cir. 2017). Moreover, "even if it was obvious to experiment with [certain] options," an invention is not obvious where "there is nothing to indicate that a skilled artisan would have had a reasonable expectation that such an experiment would succeed." *Leo Pharm. Prods., Ltd. v. Rea*, 726 F.3d 1346, 1357 (Fed. Cir. 2013) (internal citation and quotation marks omitted). Here, the record establishes that developing a generalized multi-dose regimen using an LAI to initiate therapy was an unpredictable process. As Dr. Wermeling acknowledged, there were "a large number of possibilities for combining" the dose amounts disclosed in the '548 Protocol with "different injection sites." Trial Tr. (Wermeling) at 473:19–474:19. He further testified that different injection sites, dosing intervals, and dose amounts can affect therapeutic blood levels. *Id.* at 279:3–8; 312:7–16. While Dr. Wermeling opined that the WO'384 Publication disclosed a safe and effective dosing range of 25 to 150 mg-eq., he did not credibly explain how a POSA could expect to develop effective multi-dose treatment regimens, such as those claimed in the '906 Patent, from this range. *Id.* at 321:23–322:13. Indeed, as noted above, Dr. Wermeling clearly stated that the WO'384 Publication itself "does not disclose anything about a dosing regimen," does not discuss deltoid or gluteal administration, and

does not "point you in the direction of giving a Day 1 dose of 150 mg equivalents in the deltoid and a second dose in the deltoid of 100 mg equivalents on Day 6 to 10." *Id.* at 511:15–512:8.

The record further indicates that, in contrast to single doses, multi-dose regimens must account for effects like "accumulation" and "fluctuations [in a patient's blood levels] between administrations." Trial Tr. (Sinko) at 1597:17–1600:10. Therefore, to successfully arrive at a multi-dose regimen based on the prior art, a POSA would need safety, efficacy, and pharmacokinetic data in order to evaluate how a generalized dosing regimen would perform in patients. *See Id.* at 1583:24–1584:16 (noting that without "this triumvirate of pharmacokinetics, efficacy and safety [data], you have no way to understand if some random combination of elements would lead to an effective dosing regimen"). The prior art, however, contained no such data. *Id.* at 1582:19–1583:18. While Dr. Wermeling testified that the '548 Protocol involved a Phase III trial, which is a clinical trial that "use[s] doses that are thought to be safe and effective," he admitted that this reference is "a protocol without any results." Trial Tr. (Wermeling) at 316:4–23, 423:20–21. Moreover, as Dr. Wermeling conceded, "most drugs fail" the drug development process. *Id.* at 543:7–10. On these facts, and given the difficulty the Janssen inventors encountered during the invention process described in detail above, the Court finds that the unpredictability of the art weighs against a reasonable expectation of success. *See Sanofi v. Watson Lab'ys Inc.*, 875 F.3d 636, 641, 646–50 (Fed. Cir. 2017) (affirming finding of no reasonable expectation of success where prior art disclosed large-scale clinical trial's hypothesis but not results); *Endo Pharm. Inc. v. Actavis LLC*, 922 F.3d 1365, 1377 (Fed. Cir. 2019) (noting that finding of no reasonable expectation of success was "further supported by the fact that the inventors of the '779 patent

engaged in extensive experimentation, involving much failure, to ultimately produce the oxymorphone of the Asserted Claims").

In addition, a POSA would not have had a reasonable expectation of successfully initiating treatment with LAI loading doses in view of the prior art. For instance, as discussed above, the Gibaldi reference on which Dr. Wermeling relies expressly teaches that "[d]epot injections are . . . indicated for maintenance treatment rather than initiation of therapy." DTX-91 at 5. Moreover, as set forth in detail below, both parties' experts agreed that the traditional dosing paradigm for treating schizophrenia used lower initial doses followed by slow upward adjustments. *See, e.g.*, Trial Tr. (Kahn) at 168:19–169:5 (for dosing risperidone, it is "recommended" to begin with an "initial dose" and then "work your way up in small increments until you get to your target dose or your effective dose range"); Trial Tr. (Kohler) at 1905:12–17 (explaining that the initial dose of Risperdal Consta "was limited to 25 milligrams or less, which was in many people not the eventual dose required to manage the psychosis," followed by subsequent higher doses weeks later). The Goodman reference also instructed initiating low doses of risperidone and watching for side effects as dose amounts are increased. *See* DTX-93 at 339 ("Low doses of risperidone have been reported to attenuate negative symptoms of schizophrenia with a low incidence of extrapyramidal side effects. Extrapyramidal effects are commonly seen, however, with doses of risperidone in excess of 6 mg/day."). Even the FDA and an external panel of experts suggested that Janssen use lower initial doses. PTX-92 at 1, PFOF ¶¶ 57–58; PTX-94 at 59, 61. Contrary to the prior art teachings and traditional dosing strategy, the '906 Patent claims high-loading dose regimens using

depot injections. Thus, the Court is not persuaded that a POSA would have had a reasonable expectation of successfully achieving the claimed regimens.[31]

4. The Cleton 2008 References Support a Finding of Nonobviousness

Defendant contends that four additional references—two abstracts published in *Clinical Pharmacology & Therapeutics* in March 2008 titled "PI-74" and "PI-75" and two corresponding posters allegedly presented at an April 2008 conference (collectively, "Cleton 2008")—render Claim 2 obvious. Def. Br. at 33–34; DTX-18, -19, -20.[32] Plaintiffs counter that the Cleton 2008 references are not prior art because the claimed invention antedated them and the inventors had possession of the information disclosed in the references prior to their publication. Pls. Br. at 58–64. The Court finds that even if it considers the Cleton 2008 references, they weigh in favor of nonobviousness.[33]

[31] No additional showing has been required of Teva despite its presentation of testimony and argument concerning motivation to alter the prior art in order to achieve rapid and long-term efficacy with paliperidone palmitate. *See, e.g.*, Trial Tr. (Wermeling) at 469:2–470:13 (Dr. Wermeling agreed that the '906 Patent claims dosing regimens that provide both "rapid efficacy" and "long-term efficacy."); 311:18–23 (testifying that a POSA would be motivated to modify the '544 Patent and WO'384 Publication to "accelerate the onset of effect"); 321:1–22 (noting that a POSA "would be motivated to use the maximum effective and safe dose" when initiating treatment of an "acutely agitated" patient). Nonetheless, a party raising an argument at trial places that argument at issue. *See Immunex Corp. v. Sandoz Inc.*, 964 F.3d 1049, 1066 (Fed. Cir. 2020), cert. denied, 209 L. Ed. 2d 751 (May 17, 2021) (rejecting post-trial argument due to party's focus on challenged issue during trial).

[32] The Cleton 2008 references all reflect work done by or associated with Janssen. *See* DFOF ¶¶ 287, 298; Pls. Br. at 58–59.

[33] Janssen offers strong arguments in support of its view that Cleton 2008 is not prior art. Pls. Br. at 58–64. Janssen asserts that the claimed invention was conceived and reduced to practice in the Summer of 2007 prior to the publication of Cleton 2008, citing to testimony and evidence from Drs. Gopal and Samtani. *Id.* at 61. As discussed later in this Opinion, Janssen is seeking to add Drs. Gopal and Samtani as inventors of the '906 Patent. Janssen further contends, citing to the '918 Provisional as evidence, that the inventors had possession of the information disclosed in Cleton 2008 before these references were published. *Id.* at 63–64. Regardless, even considering the Cleton 2008 references as prior art does not alter this Court's analysis regarding obviousness.

PI-74 and its corresponding poster do not support Defendant's obviousness arguments because they relate to a single-dose, rather than multi-dose, regimen. *See* DTX-18, -19. As Dr. Wermeling noted, PI-74 "is a single dose [proportionality] study" in which "[e]ach subject received a single injection of paliperidone palmitate" in "either the deltoid or the gluteal muscle." Trial Tr. (Wermeling) at 378:3–12; *see also* DTX-18, -19. Unlike the dosing regimens claimed in the '906 Patent, PI-74 did not involve any loading or maintenance doses. Trial Tr. (Wermeling) at 378:13–21. Moreover, Dr. Wermeling allowed that PI-74 neither contains efficacy data nor "disclose[s] giving a Day 1 loading dose of 150 mg. equivalents in the deltoid and a second loading dose in the deltoid of 100 mg. equivalents on Days 6 to 10." Trial Tr. (Wermeling) at 392:9–18.[34] As discussed above, multi-dose regimens like the claimed invention differ from single doses because they need to account for "accumulation," and "fluctuations [in a patient's blood levels] between administrations." Trial Tr. (Sinko) at 1597:17–1600:10. To develop an effective multi-dose regimen, a POSA would need efficacy data, which these references lack. *See Id.* at 1583:24–1584:16, 1605:17–1606:25. Thus, when viewed as a whole, the Court cannot say that this reference renders the claimed invention obvious.

Similarly, the Court finds that PI-75 and its corresponding poster would not change the obviousness analysis. PI-75 concerns a "fixed-dose" study of four equal doses of 100 mg-eq. of

[34] The Court also notes that Cleton 2008 would not create a reasonable expectation of success. DTX-18, -19, -20. Contrary to Defendant's assertion that "Cleton 2008 provides the confirmatory data that Dr. Sinko desired" (Def. Br. at 33), none of these references contain efficacy data. *See* Trial Tr. (Wermeling) at 392:9–13, 408:23–25; Trial Tr. (Sinko) at 1603:11–20; DTX-18, -19, -20. At most, Cleton 2008 discloses average pharmacokinetic data, not patient-level data. Without efficacy data, a POSA would "have to do . . . controlled clinical studies to prove that those [target blood] levels were actually effective." Trial Tr. (Sinko) at 1540:5–1541:9; *see also id.* at 2134:1–2134:11 (noting that "the correlation between the target range and what a clinical investigator determines is efficacy is not straightforward" and the two "may not be linked"). Thus, the Court finds that Cleton 2008 does not change the above analysis.

paliperidone palmitate administered in either the deltoid or gluteal muscle on days 1, 8, 36, and 64. DTX-18; Trial Tr. (Wermeling) at 394:6–395:4. Similar to PI-74, PI-75 does not contain any efficacy data that would motivate a POSA to modify the reference's equal dose regimen to arrive at the dose regimens claimed in the '906 Patent. Trial Tr. (Sinko) at 1603:11–20, 1604:7–10; *see also* Trial Tr. (Wermeling) at 396:10–16 (conceding that "PI-75 [does not] give any indication as to whether the first dose of 100 mg equivalence was effective or ineffective"). Moreover, PI-75 and its corresponding poster would dissuade a POSA from using deltoid injections. Indeed, as Dr. Wermeling allowed, PI-75 disclosed "more fluctuation in drug content in the blood" and "more variation in drug absorption between different individuals when they were injected in the deltoid as opposed to the gluteal muscle." Trial Tr. (Wermeling) at 397:12–21. The corresponding poster makes similar disclosures. *See* DTX-20 at 6–7 (noting higher incidence of adverse events, "clinically relevant difference" in injection site pain, and greater fluctuation index for deltoid treatment group compared to gluteal treatment group). As Dr. Sinko credibly explained, a POSA would "want to keep . . . fluctuations at a minimum because that means changes in blood levels," which can "correspond[to] . . . toxicity." Trial Tr. (Sinko) at 1601:13–21, 1605:7–14. Accordingly, given the "higher fluctuation index and larger subject variability," a POSA considering PI-75 "would not look at injecting into the deltoid." *Id.* at 1605:7–14. Thus, the Court finds that the Cleton 2008 references support a finding of nonobviousness.[35]

5. Objective Indicia of Nonobviousness

As part of its obviousness analysis, the Court must also consider evidence regarding objective considerations of nonobviousness when present. *In re Cyclobenzaprine Hydrochloride*

[35] Defendant also contends that the claimed regimens are obvious in view of another poster reporting on the results of the SCH-201 Phase II trial ("Kramer"). *See* Def. Br. at 17–18, 30. Plaintiffs assert that the Court should not consider Kramer because: (1) it was not disclosed in Defendant's obviousness contentions, expert reports, or the trial testimony of its experts; and (2) it

Extended-Release Capsule Patent Litig., 676 F.3d 1063, 1075–77 (Fed. Cir. 2012). Such evidence is used to "guard against slipping into use of hindsight, . . . and to resist the temptation to read into the prior art the teachings of the invention in issue." *Graham*, 383 U.S. at 36 (internal citation and quotation marks omitted). Secondary considerations such as unexpected results, commercial success, long felt but unsolved needs, and the failure of others may be relevant indicia of nonobviousness. *See id.* at 17–18; *Eli Lilly & Co. v. Zenith Goldline Pharm., Inc.*, 471 F.3d 1369, 1380 (Fed. Cir. 2006). Moreover, evidence of copying, industry praise, and skepticism may also be considered. *See Diamond Rubber Co. v. Consol. Rubber Tire Co.*, 220 U.S. 428, 441 (1911); *WBIP, LLC v. Kohler Co.*, 829 F.3d 1317, 1335 (Fed. Cir. 2016); *Geo. M. Martin Co. v. Alliance Mach. Sys. Int'l LLC*, 618 F.3d 1294, 1304–05 (Fed. Cir. 2010).

Plaintiffs presented evidence of certain objective indicia that they argue support a finding of nonobviousness. A number of witnesses opined on the existence of these objective indicia including, for the Plaintiffs, (1) Dr. Srihari Gopal; (2) Dr. An Vermeulen; (3) Dr. Mahesh Samtani; (4) Dr. Christian Kohler; and (5) Ms. Carla Mulhern (Final Pretrial Order at 29–31, 38); and for the Defendant, (1) Dr. René Kahn; and (2) Mr. Ivan Hofmann (Final Pretrial Order at 39, 43).[36] While both parties offered evidence on the issue of secondary considerations, the burden always remains on Defendant to prove by clear and convincing evidence that the claimed invention is obvious. *In re Cyclobenzaprine Hydrochloride,* 676 F.3d at 1075–79 (concluding that, when considering secondary considerations of nonobviousness, the burden never shifts to the patentee

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was found not to be prior art in a parallel foreign litigation in Canada. Pls. Reply at 14–15, 23–24. While the Court acknowledges Janssen's assertions and fairness concerns, even considering the Kramer reference, the Court's obviousness analysis would be unaltered because, unlike the '906 Patent, Kramer discloses equal doses injected into the gluteal muscle only.

[36] These witnesses' relevant backgrounds and qualifications have been described in earlier sections of this Opinion.

to prove nonobviousness and instead always remains on the party challenging the validity of the patent to prove by clear and convincing evidence that the patent at issue is obvious).

As to the objective indicia, Defendant challenges whether there is a sufficient nexus between the merits of the claimed invention and the objective evidence. Plaintiffs counter that the appropriate nexus between the objective evidence and the claims of the '906 Patent is present. Here, the Court finds that the secondary considerations have a sufficient nexus to the claimed invention because the proffered evidence is linked to the high loading dose deltoid injections and subsequent maintenance injections described in the '906 Patent.[37] *See WBIP, LLC*, 829 F.3d at 1330 (internal citations and quotation marks omitted) ("Where the allegedly obvious patent claim is a combination of prior art elements, we have explained that the patent owner can show that it is the claimed combination as a whole that serves as a nexus for the objective evidence; proof of nexus is not limited to only when objective evidence is tied to the supposedly 'new' feature(s)."); *Tokai Corp. v. Easton Enters., Inc*., 632 F.3d 1358, 1369–70 (Fed. Cir. 2011) (concluding that, to establish a nexus to the merits of a claimed invention, the offered secondary consideration must actually result from what is both claimed and novel in the patent). To the extent more specific arguments concerning nexus were made by the parties, such assertions are addressed in the relevant sections.

a) Unexpected Results

Unexpected or surprising results can support nonobviousness. To demonstrate unexpected results, a party must "show that the claimed invention exhibits some superior property or advantage that a person of ordinary skill in the relevant art would have found surprising or unexpected." *In*

[37] Because the Court finds that there is a nexus between the claimed invention and the objective indicia, the Court need not address Janssen's argument that a presumption of nexus should apply here (Pls. Br. at 42).

re Soni, 54 F.3d 746, 750 (Fed. Cir. 1995). "The principle applies most often to the less predictable fields, . . . where minor changes in a product or process may yield substantially different results." *Id.* Furthermore, "when unexpected results are used as evidence of nonobviousness, the results must be shown to be unexpected compared with the closest prior art." *Kao Corp. v. Unilever U.S., Inc.*, 441 F.3d 963, 970 (Fed. Cir. 2006) (internal citation and quotation marks omitted). Plaintiffs assert that the claimed dosing regimens produced the unexpected outcome of a second-generation LAI that successfully treated schizophrenia and other psychotic disorders without the need for oral supplementation, due to the dosing regimens' use of high initial loading doses to achieve rapid efficacy and monthly maintenance doses to achieve sustained efficacy. Pls. Br. at 45–46. Defendant disagrees that these properties were unexpected. Def. Br. at 54–58.

The Court finds that the Representative Claims led to unexpected results. Prior to the invention of Invega Sustenna, the conventional wisdom for both first-generation and second-generation antipsychotics was to "start low and go slow." PFOF ¶ 163 (internal citation and quotation marks omitted). Indeed, experts for both Plaintiffs and Defendant agreed that the traditional dosing paradigm for treating schizophrenia involved beginning with lower doses and slowly making upward adjustments. *See* Trial Tr. (Kahn) at 168:19–169:5 (for dosing risperidone, it is "recommended" to begin with an "initial dose" and then "work your way up in small increments until you get to your target dose or your effective dose range"), 2392:23–2393:1 (according to label, "the preferred approach" for dosing haloperidol decanoate "is to begin with lower initial doses and to adjust the dose upward as needed"); Trial Tr. (Kohler) at 1905:12–17 (explaining that initial dose of Risperdal Consta "was limited to 25 milligrams or less, which in many people was not the eventual dose required to manage the psychosis," followed by subsequent higher doses weeks later). Moreover, as the Gibaldi prior art reference indicated, "[d]epot

injections are long-acting dosage formulations indicated for maintenance treatment rather than initiation of therapy." PTX-64 at 5. The claimed dosing regimens run contrary to these prior art teachings because they use depot injections of high, rather than low, loading doses to initiate treatment.

In addition, as explained above, the claimed invention also led to unexpected results in view of the '548 Protocol prior art reference. In multi-dose regimens, such as those covered by the Representative Claims, there are many possible combinations of dose amounts, schedule, and sites of administration. PFOF ¶ 248. The '548 Protocol, which Defendant identifies as one of the closest prior art references, tested three different combinations of equal doses of paliperidone palmitate administered in the gluteal muscle and failed to properly initiate treatment in a rapid manner to aid with treatment adherence. *Id.* ¶ 249. By contrast, the '906 Patent regimens, which are comprised of high loading doses that must be administered in the deltoid muscles for the first two doses, succeeded. *Id.* ¶ 60. Therefore, the Court finds that in view of the prior art, the claimed invention led to unexpected results.

Defendant's primary argument against a finding of unexpected results is that "the alleged difficulties Janssen faced during development were avoidable." Def. Br. at 55. This argument is unpersuasive. As set forth above, Plaintiffs' inventors expected the Phase III clinical trials to be a success, especially because they built on the promising results of the SCH-201 study, which showed rapid efficacy. PFOF ¶ 36. Contrary to their expectations, however, the inventors encountered several clinical failures during Phase III, including a "high dropout rate" of patients discontinuing treatment because of "lack of efficacy." Trial Tr. (Vermeulen) at 784:3–10, 793:12–794:5; *see also* PTX-284 at 66–67. The evidence at trial showed that Invega Sustenna improved patient treatment adherence through its use of high initial loading doses that rapidly achieved

therapeutic concentrations of paliperidone palmitate and monthly loading doses which maintained these concentrations. Trial Tr. (Kohler) at 1910:9–1912:13 (Dr. Kohler providing a detailed and persuasive analysis of the benefits of Invega Sustenna); *see also* PTX-627 at 51. Such a "difference between an effective and safe drug and one with significant side effects that caused many patients to discontinue treatment" has been found to "constitute an unexpected difference in kind." *Allergan, Inc. v. Sandoz Inc.*, 796 F.3d 1293, 1307 (Fed. Cir. 2015). Thus, the unexpected results indicator weighs in favor of nonobviousness.

b) Skepticism

"Evidence of industry skepticism" is relevant to the obviousness inquiry. *WBIP, LLC*, 829 F.3d at 1335. "If industry participants or skilled artisans are skeptical about whether or how a problem could be solved or the workability of the claimed solution, it favors non-obviousness." *Id.* The Federal Circuit has "recognize[d] a range of third-party opinion that can constitute skepticism," including "testimony that third parties were 'worried' or 'surprised'" as "sufficient to establish skepticism." *Neptune Generics, LLC v. Eli Lilly & Co.*, 921 F.3d 1372, 1378 (Fed. Cir. 2019) (citing *Circuit Check Inc. v. QXQ Inc.*, 795 F.3d 1331, 1337 (Fed. Cir. 2015)).

Here, Plaintiffs have proffered evidence of skepticism that supports a finding of nonobviousness. The trial record indicates that on February 28, 2007, in response to Janssen scientists' proposal of the dosing regimen of 150 mg-eq. on the first day of treatment and 100 or 50 mg-eq. on the eighth day, a panel of external advisors "expressed their opinion" that a lower dosing regimen with "lesser risk" should be considered. PTX-92 at 1.

These external advisors were not the only industry participants to express doubt regarding aspects of the claimed invention. Indeed, after Janssen initially applied for regulatory approval of a dosing regimen of "100/100 mg-eq., day 1/8, deltoid dosing regimen" in October 2007, the FDA suggested that Janssen use even lower initiation doses starting at 75 mg-eq. up to 100 mg-eq. on

the first and eighth days of treatment. PFOF ¶¶ 57–58; PTX-94 at 59, 61. Although the FDA's recommendation comported with the "start low, go slow" conventional wisdom of the time (*see* PTX-808 at 3 (internal quotation marks omitted)), it also evidenced skepticism toward the high-loading dose strategy later claimed in the '906 Patent.

Moreover, even after Invega Sustenna received FDA approval, treating psychiatrists had reservations about the claimed dosing regimens. *See* Trial Tr. (Kohler) at 1907:2–1908:4 (credibly explaining that when Invega Sustenna first became available, psychiatrists found the treatment initiation guidelines "unusual," "very different from what we had been familiar and, to some extent, comfortable with," and thought it might "lead to side effects that would prevent the person from continuing with treatment"). Such concerns weigh in favor of nonobviousness. *See Neptune Generics, LLC*, 921 F.3d at 1378 (affirming finding of skepticism based on FDA concerns); *Cir. Check Inc.*, 795 F.3d at 1337 (testimony that customers were "worried" about using claimed invention supported finding of skepticism).

Defendant's arguments against a finding of skepticism are unpersuasive. Defendant contends that Plaintiffs have failed to establish skepticism because: (1) they rely on inadmissible hearsay from fact witness testimony; and (2) the FDA's statements were merely advice in keeping with its regulatory duties, rather than skepticism. *See* Def. Br. at 52–54. With respect to Defendant's first argument, the Court finds that even if it were to exclude the testimony cited by Plaintiffs regarding the outside experts' concerns as inadmissible hearsay,[38] Plaintiffs nevertheless proffered sufficient evidence of the panel's skepticism in the form of meeting minutes. *See* PTX-

[38] Dr. Gopal testified, for example, that in regard to the 150 mg-eq. day 1 and 100 mg-eq. day 8 dosing regimen, outside experts "didn't think it was necessary. They thought it actually was risky. They thought that the dose was too high and that we should go for a lower dose." Trial Tr. (Gopal) at 1075:14–16.

92. These minutes, which relate to the February 28, 2007, "Clinical Pharmacokinetic and Dosing Advisory Board Meeting," documented the outside experts' skepticism of a high-dosing regimen, rather than, as Defendant argues, merely the probability of receiving regulatory approval. They are an admissible business record under Federal Rule of Evidence 803(6). *See* Fed. R. Evid. 803(6) (recognizing exception to rule against hearsay for records of regularly conducted activities);[39] PTX-92 at 1 (noting that compared with the "[p]roposed dosing regimen," "[a] more acceptable regimen from a regulatory viewpoint would be 100 mg eq. (Day 1) followed by either 100 or 50 mg eq. on Day 8" because it "provides therapeutic concentrations early and in a safe range").

Defendant's contention regarding the FDA's statements is similarly unavailing. According to Defendant, the FDA's suggestion of a 75 mg-eq. dose is not probative of skepticism, but instead "'reflect[ed] attention to the FDA's normal duties ensuring the safety and efficacy of new drugs.'" Def. Br. at 53 (quoting *Bayer Healthcare Pharm., Inc. v. Watson Pharm., Inc.*, 713 F.3d 1369, 1377 (Fed. Cir. 2013)). Defendant's reliance on *Bayer*, however, is misplaced. In *Bayer*, the Federal Circuit found an FDA request for efficacy and safety data regarding an element of the proposed dosing regimen insufficient to establish skepticism. *Bayer Healthcare Pharm., Inc.*, 713 F.3d at 1377. The *Bayer* court concluded that the FDA's request was in keeping with the agency's

[39] "The business records exception allows admission of records of regularly conducted activity through the testimony of a custodian or other qualified witness," if the records meet the other requirements of Federal Rule of Evidence 803(6). *Crash Dummy Movie, LLC v. Mattel, Inc.*, 601 F.3d 1387, 1392 (Fed. Cir. 2010) (citing Fed. R. Evid. 803(6)). At trial, Dr. Samtani confirmed that PTX-92 contains the minutes of Janssen's February 28, 2007, meeting with the external advisors, which he attended, and the Court finds that Plaintiffs have laid a sufficient foundation for the admission of the minutes as a business record. *See* Trial Tr. (Samtani) at 1346:16–1347:2. Furthermore, the Court finds that Defendant has not met its burden of showing that the meeting minutes "indicate a lack of trustworthiness," as required for exclusion under Rule 803(6). Fed. R. Evid. 803(6). Finally, and in any event, both parties agree that PTX-92 may be admitted to show its effect on the listener, rather than for its truth. *See* Trial Tr. (Gopal) at 1074:16–1076:3; Fed. R. Evid. 801(c)(2) (excluding only out-of-court statements offered "to prove the truth of the matter asserted in the statement"). Therefore, the Court will consider the minutes in its analysis.

regulatory duties "requiring actual data to corroborate statements in a new drug application" and "in no way indicates that FDA experts would have been surprised to receive such data." *Id.* Here, by contrast, the FDA's statement is not a simple request for data, but rather a recommendation to move away from the high-loading dose strategy proposed by Janssen. *See* PTX-94 at 59, 61. As the FDA's suggestion concerned aspects of the invention at issue, the Court finds that it is evidence of industry skepticism and weighs in favor of nonobviousness. *See Neptune Generics, LLC*, 921 F.3d at 1378 (affirming skepticism finding based on FDA's disagreement with patentee's proposed course of action during clinical trial).

c) Praise

"Evidence that the industry praised a claimed invention or a product which embodies the patent claims weighs against an assertion that the same claim would have been obvious. Industry participants, especially competitors, are not likely to praise an obvious advance over the known art." *WBIP, LLC*, 829 F.3d at 1334; *see also Institut Pasteur & Universite Pierre Et Marie Curie*, 738 at 1347 (noting that "industry praise . . . provides probative and cogent evidence that one of ordinary skill in the art would not have reasonably expected [the invention at issue]"). Plaintiffs identify several sources of industry praise in support of their position, including Dr. Kohler's testimony that Invega Sustenna is his "first choice" LAI, trade publication articles, an FDA employee's remarks at a 2013 industry conference, and Invega Sustenna's nomination for the Prix Galien award. Pls. Br. at 49–50; PFOF ¶ 208. The Court finds that certain of the cited trade publications are the most probative evidence of praise, while affording lesser weight to others.

At trial, Plaintiffs introduced articles touting the benefits of Invega Sustenna. One such article is titled "New Label for LAI Paliperidone Breaks FDA Ground by Including Real-World Data" from the trade publication *Psychiatric News*. This article noted that the results of the Paliperidone Palmitate Research In Demonstrating Effectiveness study indicated that "the average

time before any treatment failure was about six months longer in the LAI group compared with the oral antipsychotic group." PTX-131 at 1, 3. According to the article, "[t]he improvements seen were due in part to better adherence rates of the medication, which is an advantage of LAIs as the medication is administered at clinics." *Id.*; *see also* PFOF ¶ 206. Another article, published by Thomas R. Einarson et al. in the *Journal of Medical Economics*, stated that "[s]ince [paliperidone palmitate]-LAI is the drug with the lowest cost per patient treated and the highest number of [quality adjusted life years], it dominates the other two atypical antipsychotic depots" and "should be considered the drug of choice in many situations." PTX-134 at 5. While Defendant asserts that the results discussed in Einarson were limited to the Czech Republic (*see* Def. Br. at 50–51), the Court finds that the article nevertheless amounts to praise of the claimed invention.

Plaintiffs point to two other articles as evidence of industry praise. Pls. Reply Br. at 41. The first article, "Efficacy and Safety Profile of Paliperidone Palmitate Injections in the Management of Patients with Schizophrenia: An Evidence-Based Review" (PTX-133), reported on clinical trials confirming the importance of Invega Sustenna's high initial loading doses. *See* Trial Tr. (Kahn) at 2412:9–20. The second article, "Paliperidone palmitate: a new long-acting injection for schizophrenia" (PTX-506), noted advantages to using Invega Sustenna over Risperdal Consta. *See* Trial Tr. (Kahn) at 2422:1–4. Defendant notes that both articles were funded or reviewed by Janssen. *See* Def. Br. at 51. Nevertheless, the Court acknowledges Plaintiffs' contention that these articles were peer-reviewed and data driven (*see* Pls. Reply Br. at 41) and finds that Defendant has not provided persuasive evidence of bias or improper influence by Janssen sufficient to reject these articles entirely.

Similarly, Janssen argues that the selection of Invega Sustenna as a finalist for the Prix Galien award is evidence of industry praise. Pls. Br. at 49. The Court acknowledges the Prix

Galien is an important award that has been compared to the Nobel Prize in the pharmaceutical world. PFOF ¶¶ 188, 208. While Teva raised issues regarding who nominated Invega Sustenna for this award, the Court gives some weight to this item given Janssen was a finalist.[40] *See, e.g.*, *Genzyme Corp. v. Dr. Reddy's Lab'ys, Ltd.*, No. 13-1506, 2016 WL 2757689, at *15 (D. Del. May 11, 2016), aff'd, 716 F. App'x 1006 (Fed. Cir. 2017).

d) Copying

It is well settled that the copying of an invention can be indicative of nonobviousness. *Diamond Rubber*, 220 U.S. at 440–41 (finding "imitation" of a certain tire as a "concession to its advance beyond the prior art and of its novelty and utility"). Generally, copying is not considered evidence of nonobviousness in the ANDA context "because a showing of bioequivalence is required for FDA approval." *Bayer Healthcare Pharm., Inc.*, 713 F.3d at 1377 (citing *Purdue Pharma Prods. L.P. v. Par Pharm., Inc.*, 377 F. App'x 978, 983 (Fed. Cir. 2010)). Copying may, however, be probative of nonobviousness where the generic manufacturer "rel[ies] on the accused process." *Merck Sharp & Dohme Corp. v. Hospira, Inc.*, 874 F.3d 724, 728, 731 (Fed. Cir. 2017) (finding evidence of copying where defendant "tried five alternative formulations in an attempt to avoid copying" before relying on patent owner's process because the "[Hatch-Waxman] Act does not . . . require the generic manufacturer to copy the NDA holder's process of *manufacturing* the drug"); *see also Dey, L.P. v. Teva Parenteral Meds., Inc.*, 6 F. Supp. 3d 651, 681 (N.D.W. Va. 2014), *aff'd sub nom. DEY LP v. Teva Parenteral Meds., Inc.*, 600 F. App'x 773 (Fed. Cir. 2015) (Copying was established where "Teva could have developed its own solution using different excipients, but instead chose to reverse engineer Dey's formulation based on Dey's patents. This

[40] To the extent that Invega Sustenna's market share is also presented as evidence corroborating industry praise of the drug as a "first choice" LAI (Pls. Br. at 49), the Court discusses this factor in its commercial success analysis.

provides a strong indication that the prior art provided Teva with no obvious alternative to Dey's invention.").

Here, Plaintiffs have proffered evidence of copying and the Court affords some limited weight to this factor to support the nonobviousness conclusion the Court independently reaches. In its ANDA submission, Defendant stated that the [redacted] PTX-26 at 176; PFOF ¶ 209. While Defendant contends that it [redacted] (DFOF ¶ 528), [redacted] *See* Trial Tr. (Sinko) at 1625:1–6 [redacted]; *see also* PFOF ¶ 209. Absent such a requirement, [redacted] the claimed invention. *See Merck Sharp & Dohme Corp.*, 874 F.3d at 728, 731; *Dey, L.P.*, 6 F. Supp. 3d at 681.

In addition, Defendant argues that there is no evidence of copying because before it filed its ANDA, "Janssen submitted a Citizen's Petition to the FDA seeking a heightened bioequivalence standard that, if granted, would serve to implicitly regulate the particle size of Teva's ANDA product." Def. Br. at 46. This argument is similarly unavailing. The record contains no evidence that the FDA responded to the petition, and, as of the date of this decision, the petition appears to remain pending. Thus, because the petition has not imposed particle size regulations on generic manufacturers, it does not weaken the evidence of copying.[41]

[41] Defendant cites *Liqwd, Inc. v. L'Oreal USA, Inc.*, 941 F.3d 1133, 1138 (Fed. Cir. 2019) to argue that the similarities between the particle sizes of its generic product and Invega Sustenna and the '906 Patent are not probative of copying. Def. Br. at 47. While the court in *Liqwd, Inc.* did note

e) Long-Felt Need and Failure of Others

"The existence of a long-felt but unsolved need that is met by the claimed invention is . . . objective evidence of non-obviousness." *Millennium Pharm., Inc. v. Sandoz Inc.*, 862 F.3d 1356, 1369 (Fed. Cir. 2017); *see also WBIP, LLC*, 829 F.3d at 1332 ("Evidence of a long felt but unresolved need tends to show non-obviousness because it is reasonable to infer that the need would have not persisted had the solution been obvious."). In order to show satisfaction of long-felt need, one must establish that (1) a POSA recognized a problem that existed for a long period of time without a solution; (2) the long-felt need had not been satisfied by another before the claimed invention; and (3) the invention in fact satisfied the long-felt need. *See Newell Cos., Inc. v. Kenney Mfg. Co.*, 864 F.2d 757, 768 (Fed. Cir. 1988); *In re Cavanagh*, 436 F.2d 491, 495–96 (C.C.P.A. 1971); *In re Gershon*, 372 F.2d 535, 538–39 (C.C.P.A. 1967).

The trial evidence showed that the claimed invention satisfied the long-felt need for an LAI that could successfully initiate and maintain treatment without oral supplementation. Prior to the invention of Invega Sustenna, all antipsychotics on the market had significant limitations. For example, first-generation antipsychotics had unfavorable side effect profiles and required oral pretreatment and individualized dosing. PFOF ¶¶ 15–18. Similarly, Risperdal Consta, the only second-generation LAI to predate Invega Sustenna, provided only two weeks of therapeutic benefits and required oral supplementation for the first three weeks of treatment. *Id.* ¶¶ 19–20. These limitations contributed to patient non-adherence, a significant barrier to treatment. *Id.* ¶¶ 14,

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that "more is needed than merely showing that similarity exists between the patent and the competitor's accused product," it nevertheless went on to explain that "access to an *issued patent* coupled with circumstantial evidence regarding changes to a competitor's design is sufficient to support copying." *Liqwd, Inc.*, 941 F.3d at 1137–38 (internal citation omitted). [redacted] PTX-26 at 176. Thus, the record here discloses more than mere similarities between the parties' products.

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17–20. Thus, as Drs. Kahn and Kohler testified, prior to Invega Sustenna, none of the second-generation treatments on the market were able to provide monthly dosing without the need for oral supplementation. *See* Trial Tr. (Kahn) at 2410:8–17 (agreeing that "there [were] no second-generation antipsychotics that were dosed monthly without the need for oral supplementation"); Trial Tr. (Kohler) at 1910:6–1912:19 (describing clinical benefits of Invega Sustenna and noting that "none of the previous long-acting injectables were able to provide all these benefits").

Contemporaneous documentary evidence confirmed the need for an LAI that could achieve the benefits that Invega Sustenna provides. Indeed, in an email dated September 22, 2006, a Janssen clinician noted that the then-used dosing regimens were "not getting sufficient numbers of subjects into a therapeutic range early enough" and that "[i]t is not sufficient to say that they get there by day 22 or 36 - that is too late for subjects with schizophrenia and will not lead to the efficacy that this product needs to have in the market place." PTX-812 at 1; PFOF ¶ 174. During the paliperidone palmitate project development process, Janssen made it its goal to overcome these treatment limitations. *See* PFOF ¶ 21; Trial Tr. (Vermeulen) at 751:13–23 (explaining that the "target protocol" for the project was "to have a better product that started releasing quickly after injection and then not need supplementation"); PTX-166 at 19.

The '906 Patent fulfilled this long-felt need. As Drs. Sinko and Kohler agreed, Invega Sustenna is an LAI that initiates and maintains therapeutic levels of paliperidone palmitate without oral supplementation. *See* Trial Tr. (Sinko) at 1473:3–5; Trial Tr. (Kohler) at 1911:9–22. Unlike earlier treatment options, Invega Sustenna is a well-tolerated medication that uses a uniform initiation regimen. *See* Trial Tr. (Kohler) at 1910:6–1912:19. Moreover, it has "improved adherence" among patients. *Id.* at 1912:8–9; *see also* PTX-627 at 51. While Defendant relies on Dr. Kahn's testimony to argue that the claimed invention did not resolve any long-felt need (*see*

Def. Br. at 61), Dr. Kahn's testimony is unsupported by the record. According to Dr. Kahn, "the major change" in schizophrenia treatment "occurred in the mid-1950s," when chlorpromazine, the first antipsychotic, was introduced. Trial Tr. (Kahn) at 2296:15–17. Since that time, Dr. Kahn asserted, "even though many antipsychotics ha[ve] been introduced, it hasn't materially changed the outcome in schizophrenia." Trial Tr. (Kahn) at 2296:22–24. These contentions, however, are contradicted by a reference relied on by Defendant's other expert Dr. Wermeling and the prescription frequency data for various medications. *See* DTX-104 at 5 (explaining that "Chlorpromazine and other first-generation antipsychotics . . . do not improve and may even exacerbate the negative symptoms of schizophrenia and are associated with dose-limiting extrapyramidal symptoms (EPS)"); PTX806B at 66–73 (chart showing total days of treatment for various schizophrenia medication from 2015 through 2018); *see also* PFOF ¶¶ 178–79. Thus, in view of the trial record as a whole, and the fact that Defendant did not credibly rebut Dr. Sinko's assertion that Invega Sustenna practices Representative Claims 2, 19, 20, and 21 when dosed in accordance with its label, the Court finds that the objective indicator of long-felt need weighs in favor of nonobviousness. *See* Trial Tr. (Sinko) at 1610:8–1614:19; Trial Tr. (Kahn) at 2337:1–2338:16, 2344:2–18; *Eli Lilly & Co.*, 471 F.3d at 1380 (finding of "need for a safer, less toxic, and more effective" alternative to existing treatment options provided a basis for unmet need); *WBIP, LLC*, 829 F.3d at 1331 (holding that a nexus can be presumed when the asserted objective indicia is tied to a specific product and the product is the invention claimed in the patent).

f) Commercial Success

"The commercial response to an invention is significant to determinations of obviousness. . . ." *Demaco Corp. v. F. Von Langsdorff Licensing Ltd.*, 851 F.2d 1387, 1391 (Fed. Cir. 1988). For evidence of commercial success to be accorded significant weight, there must be "a nexus between the claimed invention and the commercial success." *Ormco Corp. v. Align Tech., Inc.*,

463 F.3d 1299, 1312 (Fed. Cir. 2006). The claimed invention need not, however, be "solely responsible for the commercial success, in order for this factor to be given weight appropriate to the evidence." *Cont'l Can Co. USA, Inc. v. Monsanto Co.*, 948 F.2d 1264, 1273 (Fed. Cir. 1991).

Here, Plaintiffs demonstrated that the claimed dosing regimens contributed to Invega Sustenna's commercial success. The record indicates that, when adjusted for rebates and discounts, Invega Sustenna's net sales in the United States have grown annually since its launch in 2009 and have exceeded $1 billion from 2015 through 2019. PTX-8, -9, -806B at 3; Trial Tr. (Mulhern) at 2579:11–2580:1; Trial Tr. (Hofmann) at 2741:24–2742:7, 2833:18–2834:21. Furthermore, Invega Sustenna has accounted for over 50 percent of all revenue generated by sales of LAI antipsychotics in the United States annually from 2013 through 2019. PTX-806B at 91–92.[42] In the fourth quarter of 2019 alone, Invega Sustenna had 30.9 percent of the market share based on days of treatment among second-generation long-acting treatments—more than twice the share of its closest competitor. *Id.* at 37 (noting next closest competitor Abilify Maintena had 12.6 percent fourth quarter 2019 market share based on days of treatment). Defendant's economic expert did not dispute the underlying market data relied on by Plaintiffs (*see* Trial Tr. (Hofmann) at 2741:22–2742:7, 2833:18–2835:8, 2836:18–22), and Plaintiffs' economic expert opined that "[b]ased on [her] review of the economic evidence, it's quite clear that Invega Sustenna has achieved substantial success in the marketplace no matter how you look at it, sales or market penetration" (Trial Tr. (Mulhern) at 2586:2–5). *See also* Trial Tr. (Hofmann) at 2838:10–21 (agreeing that none of the competing LAIs introduced after Invega Sustenna's launch "has

[42] The LAI antipsychotic market consists of two first-generation and eight second-generation products. PTX-806B at 91–92; PFOF ¶ 188.

managed to displace Invega Sustenna from its position as the best-selling second-generation antipsychotic[] in the United States").

The record further establishes that the benefits of the patented dosing regimens contributed to Invega Sustenna's success on the market. At trial, Defendant's economic expert did not refute Janssen's assertion that Invega Sustenna's dosing regimen consisting of a monthly injectable without oral supplementation "is a factor contributing to [its] marketplace performance." Trial Tr. (Hofmann) at 2852:17–2853:7. Janssen highlighted these features in its marketing materials, which, as Plaintiffs' expert, Carla Mulhern, credibly opined, suggests that they were viewed as "the key differentiators that distinguish their product from the competition." Trial Tr. (Mulhern) at 2594:12–21. Indeed, Janssen's "[c]ore [m]essage" for Invega Sustenna emphasized that "patients can receive two starting doses . . . in 7 days with rapid & sustained plasma-levels for up to one month and no need for oral supplementation." PTX-416 at 33; *see also, e.g.*, PTX-395 at 6, -417 at 76, -456 at 111. Furthermore, market research indicated that the claimed benefits "are differentiators for healthcare providers." Trial Tr. (Mulhern) at 2597:8–2598:6; PTX-410, -412, -415, -417, -421.

In addition, LAI market data demonstrates that the patented benefits helped contribute to Invega Sustenna's commercial success. The record establishes that paliperidone palmitate is the only second-generation antipsychotic whose market share is greater for its long-acting form than for its short-acting oral form. Trial Tr. (Mulhern) at 2599:8–18 ("Invega Sustenna has substantially outperformed the performance of the paliperidone molecule in the short-acting segment, and this stands apart from the other molecules in the long-acting space. We can see – for most of them, we see the opposite relationship."). Indeed, it holds approximately 31 percent of the long-acting market share compared to about 1 percent of the short-acting market share. Trial Tr. (Mulhern) at

2600:5–7; PTX-454, -806B at 74–81. The difference in paliperidone palmitate's short- and long-acting market shares indicates "that there is something besides the molecule that is explaining or contributing to the success of Invega Sustenna." Trial Tr. (Mulhern) at 2599:19–21.

Defendant asserts that Invega Sustenna's commercial success can be attributed to factors other than the claimed dosing regimens, such as Janssen's marketing efforts, its industry reputation, its rebates and sampling program, and off-label usage of the product.[43] Def. Br. at 66–67; Def. Reply Br. at 29–30. This argument is unpersuasive. With respect to marketing, the trial evidence established that Janssen's promotional expenditures for Invega Sustenna were lower than that of its competitors (*see* PTX-806B at 124, Trial Tr. (Mulhern) at 2665:21–2666:4), and the marketing intensity for the product was lower than the industry average. *See* Trial Tr. (Mulhern) at 2615:16–24, PTX-806B at 9, 122–24. Moreover, Defendant's economic expert testified that he did not have any alternative data comparing the marketing activities of Janssen and its competitors. Trial Tr. (Hofmann) at 2846:5–8, 2848:13–22. While Defendant contends that Janssen's discount and rebate offers drove prescriptions of Invega Sustenna (*see* Def. Br. at 67), its economic expert conceded that he did not have data on rebates and discounts offered by Janssen's competitors (Trial Tr. (Hofmann) at 2848:17–22), and Plaintiffs' economic expert found that, based on publicly-available information, the "discounts and rebates for Invega Sustenna are in line with the pharmaceutical industry as a whole." Trial Tr. (Mulhern) at 2615:25–2616:20. Furthermore, Janssen's sampling program does not weaken the commercial success evidence because Janssen's competitors also maintain sampling programs and Defendant's economic expert did not have any data to show that Janssen's sampling efforts were stronger than its competitors' efforts. Trial Tr.

[43] Defendant's argument that blocking patents undermine the evidence of Invega Sustenna's commercial success is discussed below. Def. Br. at 60–65.

(Mulhern) at 2616:7–13; Trial Tr. (Hofmann) at 2848:9–16. Thus, the Court finds that Plaintiffs' marketing efforts did not meaningfully distinguish Invega Sustenna from its competitors. Trial Tr. (Mulhern) at 2615:25–2616:20.

Defendant's argument regarding the impact of Janssen's reputation on sales is similarly unavailing. As Plaintiffs correctly point out, Invega Sustenna has substantially outperformed other Janssen products on the market, belying Defendant's assertion that the Janssen brand is responsible for Invega Sustenna's success. Trial Tr. (Mulhern) at 2616:24–2618:1; *see also* PTX-806B at 10. Furthermore, Defendant's contentions regarding off-label usage do not overcome Plaintiffs' evidentiary showing. [redacted], which was repeatedly objected to by Janssen, the trial record as a whole indicates that Janssen's core marketing message emphasized the claimed dosing regimens (*see* PTX-416 at 33), and Plaintiffs' economic expert explained that her analysis was not based on any "explicit assumptions about whether every sale used the dosing regimen." Trial Tr. (Mulhern) at 2642:4–6. Thus, the Court finds that the off-label usage evidence does not change the above analysis or refute evidence of nexus, and the commercial success indicator as a whole supports a finding of nonobviousness.

i. *The Alleged "Blocking Patents" Do Not Undermine Evidence of Long-Felt Need or Commercial Success*

Defendant argues that evidence of Invega Sustenna's commercial success, or any long-felt need resolved by the product, is not probative of nonobviousness because three alleged blocking patents owned by Plaintiffs precluded competitors from arriving at or practicing the claimed dosing

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regimens.[44] *See* Def. Br. at 60–65; DFOF ¶ 416. On the facts of this case, the Court finds Defendant's contentions unpersuasive.

A patent is considered "a 'blocking patent' where practice of a later invention would infringe the earlier patent." *Acorda Therapeutics, Inc. v. Roxane Lab'ys, Inc.*, 903 F.3d 1310, 1337 (Fed. Cir. 2018). "Where 'market entry by others was precluded [due to blocking patents], the inference of non-obviousness of [the asserted claims], from evidence of commercial success, is weak.'" *Galderma Lab'ys, L.P. v. Tolmar, Inc.*, 737 F.3d 731, 740 (Fed. Cir. 2013) (quoting *Merck & Co. v. Teva Pharm. USA, Inc.*, 395 F.3d 1364, 1377 (Fed. Cir. 2005)) (alterations in original). The Federal Circuit has explained, however, that "the mere existence or sheer number of blocking patents does not, without more, 'necessarily detract from evidence of commercial success of a product or process.'" *Acorda Therapeutics, Inc.*, 903 F.3d at 1338 (quoting *Merck Sharp & Dohme Corp.*, 874 F.3d at 731). Rather, whether commercial success evidence should be discounted because of a blocking patent is "a fact-specific inquiry." *Merck Sharp & Dohme Corp.*, 874 F.3d at 731.

As an initial matter, Plaintiffs correctly note that Defendant did not proffer any technical expert opinion on the scope of the alleged blocking patents. *See* Pls. Br. at 50–51. Indeed, at trial, Defendant originally indicated that it intended to recall Dr. Wermeling, its obviousness expert, for rebuttal on the issue of secondary considerations. *See* Trial Tr. at 412:17–19. After Dr. Wermeling completed his initial testimony, however, Defendant advised the Court that it would not recall him

[44] The three alleged blocking patents are the '544 Patent, U.S. Patent No. 5,254,556 (the "'556 Patent"), and U.S. Patent No. 6,077,843 (the "'843 Patent"). All three patents are directed towards paliperidone palmitate. *See* DTX-157, -159, -160. Although Defendant identified U.S. Patent No. 5,352,459 (the "'459 Patent") as a fourth alleged blocking patent in a pretrial submission (*see* Final Pretrial Order at 28), it did not discuss the '459 Patent in its post-trial briefing. The Court therefore will not specifically address the '459 Patent, but notes that it would be subject to the analysis of blocking patents below.

(*id.* at 2456:23–2457:2), and instead solely relied on the opinion of Mr. Hofmann, its economic expert, on the subject of blocking patents. Mr. Hofmann admitted, however, that he was not qualified to assess the scope of the prior patents himself, that prior to trial he had considered Dr. Wermeling's reply expert report in forming his opinion, that he knew that Dr. Wermeling had not read the '556 Patent, and that he did not know whether Dr. Wermeling had analyzed the scope of the '843 Patent. Trial Tr. (Hofmann) at 2786:24–2787:2, 2788:11–14, 2798:2–6, 2812:18–22; 2813:11–16. The Court finds that these admissions considerably weaken the probative value of Mr. Hofmann's testimony.

Defendant does not dispute that Mr. Hofmann made these admissions, but instead urges the Court to find a technical foundation for his testimony from other evidence in the record, such as the '544, '556, and '843 Patents themselves, Dr. Sinko's opinions, and Janssen's representations to the FDA and USPTO. Def Br. at 63 n.14. Defendant's contentions are unavailing. Even if the Court were to assume that Mr. Hofmann had an adequate foundation for his opinions, Defendant's blocking patent arguments are nevertheless unpersuasive in light of the countervailing evidence proffered by Plaintiffs. As Plaintiffs properly note, Mr. Hofmann testified that he understood it was possible to practice Claim 2 of the '906 Patent—which, as explained above, includes the dosing regimen of Claim 1 on which Claims 20 and 21 depend—without infringing the claims of the '544 and '843 Patents. Trial Tr. (Hofmann) at 2820:23–2821:10; 2823:16–21. In other words, neither the '544 nor '843 Patent would have blocked a competitor from commercializing the claimed dosing regimens at any time.

Moreover, and in any event, even if the Court assumes that the '544, '556, and '843 Patents are blocking patents, the record demonstrates that they did not in fact deter competition in this case. Indeed, as Mr. Hofmann conceded, the governing patent infringement statute contains "a

safe harbor [provision] that allows companies to develop a drug in research and development using patented technology without infringing the patent." *Id.* at 2824:3–8; *see also* 35 U.S.C. § 271(e)(1) ("It shall not be an act of infringement to make, use, offer to sell, or sell within the United States or import into the United States a patented invention . . . solely for uses reasonably related to the development and submission of information under a Federal law which regulates the manufacture, use, or sale of drugs or veterinary biological products."). Both parties' economic experts further agreed that the drug development process can take many years, even up to a decade or longer. Trial Tr. (Hofmann) at 2823:22–2824:2; Trial Tr. (Mulhern) at 2628:21–2629:10. Given this drug development timeline and the fact that the last alleged blocking patent expired in November 2018,[45] the Court finds that these patents created little, if any, disincentives to innovate as of the claimed December 19, 2007, priority date or the December 5, 2008, application date.

Finally, the evidence presented at trial establishes that competitors in fact had incentives to develop competing products during the allegedly blocked periods, and did so. Indeed, contrary to Mr. Hofmann's testimony that "[n]o one would have an economic motivation to try and research and discover [] the alleged novelties of the '906 patent" because of Janssen's "patent fortress around paliperidone palmitate for the treatment of schizophrenia," Defendant itself filed a provisional patent application involving the purification and preparation of paliperidone palmitate on January 10, 2008. Trial Tr. (Hofmann) at 2752:15–24; PTX-813 at 1. The application noted that paliperidone is "[m]arketed under the trade name Invega" and "is an anti-psychotropic agent approved in the United States for the treatment of schizophrenia." PTX-813 at 9. Furthermore, Mr. Hofmann conceded that there was an incentive to research and develop paliperidone palmitate

[45] The '556 Patent expired on October 27, 2012, the '843 Patent expired on May 12, 2017, and the '544 Patent expired on November 10, 2018. DTX-157, -159, -160.

as of December 2007, that entities other than Janssen in fact conducted such clinical trials, and that a competitor began seeking FDA approval for an alternative risperidone LAI in 2009—ten years prior to the expiration of the patents covering Janssen's Risperdal Consta product, belying Defendant's argument that Janssen maintained a monopoly over the market. Trial Tr. (Hofmann) at 2826:19–2828:6, 2829:4–10. On these facts, the Court finds that the alleged blocking patents did not discourage innovation in this case. Therefore, Plaintiffs' evidence of commercial success and long-felt unmet need should not be discounted.

6. Presumption of Obviousness

Defendant argues that the Representative Claims should be presumed obvious because they merely recite limitations from ranges disclosed in the prior art. Def. Br. at 5–12. Janssen argues that no presumption of obviousness applies here because "the unique combinations of dose amounts, dosing schedule, injection sites and particle size range claimed in the 906 Patent go far beyond simply picking a dose amount within a range." Pls. Br. at 54. Janssen cites to *Iron Grip Barbell Co. v. USA Sports, Inc.*, 392 F.3d 1317, 1320 (Fed. Cir. 2004) to argue that where "an invention is contended to be obvious based upon a combination of elements across different references, there is no presumption, and the patent challenger must prove that there was motivation to combine." Pls. Br. at 54 (internal citations and quotation marks omitted). Plaintiffs make convincing arguments that cause the Court to question the applicability of the "range" cases here, where the claimed invention at issue is composed of a unique combination of elements that are not all easily defined with numerical values that can be found in the prior art (such as injection site, unequal loading doses, and characteristics of the paliperidone formulation). *See* Pls. Reply Br. at Moreover, the differences between the prior art and the claimed invention go beyond numerical ranges, and the invention took place in an unpredictable field of art. *See* Pls. Reply Br. at 3–8.

Regardless, even if the Court were to apply a presumption of obviousness here, Plaintiffs have proffered sufficient evidence to rebut any such presumption.

The Federal Circuit has recognized that "where there is a range disclosed in the prior art, and the claimed invention falls within that range, there is a presumption of obviousness." *Iron Grip Barbell Co.*, 392 F.3d at 1322. This presumption may be rebutted, however, "with evidence that (1) the prior art taught away from the claimed invention; (2) there were new and unexpected results relative to the prior art; or (3) there are other pertinent secondary considerations." *Allergan, Inc.*, 796 F.3d at 1305 (quoting *Galderma Lab'ys, L.P.*, 737 F.3d at 738).

Here, Plaintiffs have demonstrated that, at a minimum, the prior art taught away from the invention, the claimed dosing regimens led to unexpected results, certain elements of the dosing regimen were not known to be result-effective, there were a large number of possible combinations of the relevant claim parameters, and there are other pertinent secondary considerations that support a finding of nonobviousness. *See* Pls. Reply Br. at 9–16. As both parties' experts agreed, the traditional dosing paradigm for schizophrenia treatment involved low initiation doses followed by gradual dose increases. *See* Trial Tr. (Kahn) at 168:19–169:5, 2392:23–2393:1; Trial Tr. (Kohler) at 1905:12–17. Furthermore, the Gibaldi reference taught the use of depot injections for treatment maintenance rather than initiation. DTX-91 at 5. When Janssen inventors deviated from these teachings during Phase III, including by initiating therapy with two high-loading doses administered in the deltoid muscle, they were able to overcome the failures of the earlier clinical trials, including the '548 Protocol/PSY-3003 study, and develop successful dosing regimens. *See* PFOF ¶ 60.

Similarly, as explained above, compared to the prior art, the claimed regimens unexpectedly achieved successful initiation and maintenance treatment goals. Where the '548

Protocol taught the use of equal doses administered in the gluteal muscle and failed (*see* PFOF ¶ 249), the '906 Patent dosing regimens, comprised of high initial loading doses administered in the deltoid muscle followed by maintenance doses in either the deltoid or gluteal muscle, succeeded. Additionally, it was not known in the prior art that using a LAI in the deltoid to initiate treatment would have such a major impact on blood levels of paliperidone palmitate (Trial Tr. (Vermeulen) at 770:23–771:14) and there were so many potential combinations of the claimed dosing regimen that Janssen relied on complex modeling and simulations to make their discovery (*id.* at 756:6–23). These considerations further rebut a presumption of obviousness from applying here. *See E.I. du Pont de Nemours & Co. v. Synvina C.V.*, 904 F.3d 996, 1006 (Fed. Cir. 2018); *Allergan, Inc.*, 796 F.3d at 1305.

Other secondary considerations, discussed at length above, further rebut any alleged presumption of obviousness. Plaintiffs have proffered evidence of commercial success, industry praise and skepticism, copying, and long-felt need related to the claimed dosing regimens sufficient to support a conclusion of nonobviousness. Thus, even if the Court were to assume *arguendo* a presumption of obviousness applied here, it would not alter the Court's obviousness analysis because Plaintiffs have clearly rebutted the presumption. Having found that Teva has failed to meet its burden of showing that the '906 Patent is invalid as obvious, the Court next considers Teva's written description challenge.

B. Written Description (35 U.S.C. § 112)

A patent specification "shall contain a written description of the invention." 35 U.S.C. § 112. The specification must "reasonably convey[] to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date." *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010). The test for written description "requires an objective inquiry into the four corners of the specification from the perspective of a [POSA]." *Id.* "[W]hether

a patent complies with the written description requirement will necessarily vary depending on the context. Specifically, the level of detail required to satisfy the written description requirement varies depending on the nature and scope of the claims and on the complexity and predictability of the relevant technology." *Id.* (internal citation omitted). When reviewing a patent according to these principles, "[w]ritten description is a question of fact, judged from the perspective of [a POSA] as of the relevant filing date." *Falko-Gunter Falkner v. Inglis*, 448 F.3d 1357, 1363 (Fed. Cir. 2006) (citing *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563–64 (Fed. Cir. 1991)).

Defendant argues that the Patent-in-Suit is invalid because the specification does not provide sufficient written description of the invention described in Claims 10, 13, 20, and 21. Def. Br. at 67–70. In response, Plaintiffs contend that the specification is sufficiently detailed and that Defendant failed to prove these Claims lack adequate written description by clear and convincing evidence. Pls. Br. at 68–71.

In support of their arguments, the parties rely on the testimony of Defendant's expert Dr. Kahn and Plaintiffs' expert Dr. Kohler, whose qualifications were discussed previously in this Opinion. For the reasons set forth below, the Court finds that Defendant has failed to prove invalidity based on the written description requirement by clear and convincing evidence, and therefore the Patent-in-Suit is not invalid under 35 U.S.C. § 112.

1. Overview of the Parties' Positions

Defendant argues that Claims 10, 13, 20, and 21 (together, the "Renal Impairment Claims"), which claim a dosing regimen for administering paliperidone palmitate to a renally impaired psychiatric patient, lack written description because these Claims do not specify the severity of renal impairment addressed by the dosing regimens, with only renal impairment and mild renal impairment discussed in the '906 Patent. Def. Br. at 67–68. Defendant notes that there are only two passages in the '906 Patent specification that discuss patients with renal impairment.

One passage instructs administering loading doses of about 100/75 or 75/75 mg-eq. to patients with renal impairment. *Id.* at 68. A second passage instructs adjusting loading doses for renally impaired patients to account for increased exposure levels to paliperidone, clarifying that for patients "with ***mild*** renal impairment the loading doses should be reduced to 75 mg-eq. for the first two loading doses." *Id.* (internal citations and quotation marks omitted). In Teva's view, the '906 Patent fails the written description requirement because it does not advise how patients with moderate or severe renal impairment would be dosed. *Id.* Teva also contends that the claims are invalid because they do not provide an upper limit "in terms of degree of renal impairment or maximum dose." *Id.* at 69.

Plaintiffs' first response is procedural as they argue that Teva presented a "brand-new written description challenge at trial" that was not identified in the Final Pretrial Order and is therefore waived. Pls. Br. at 69. Janssen argues that Defendant's expert, Dr. Kahn, initially asserted that the dosing regimen in the Renal Impairment Claims contained no upper limit, but later abandoned that theory to now argue that the Claims failed to properly specify the type of renally impaired patient that can be treated with the claimed dosing regimen. *Id.* at 69; PFOF ¶¶ 225–26. While the Court acknowledges Plaintiffs' argument regarding Teva's evolving positions on this issue, this Opinion addresses the issue regardless.

Turning to the merits of Teva's written description challenge, Plaintiffs assert that the '906 Patent contemplates loading doses for patients with renal impairment that allow a physician to use medical judgment when dosing. Pls. Br. at 70. Plaintiffs further argue that a POSA would recognize the '906 Patent's focus on mild renal impairment (specifically highlighted in the specification), and would not treat a patient with moderate or severe renal impairment using Invega

Sustenna.[46] Pls. Reply Br. at 48. In addition, Plaintiffs contend that the experts agreed at trial that the renal impairment doses range from about 75 mg-eq. to an upper limit of 150 mg-eq., and that the '906 Patent contains several representative embodiments of dosing regimens for renally impaired patients. Pls. Br. at 70.

2. The Claims Relevant to the Written Description Challenge

Claim 10 of the '906 Patent covers the "dosing regimen of claim 8 wherein the sustained release formulation is an aqueous nanoparticle suspension." '906 Patent (DTX-1/PTX-1) col. 33:26–27. The dosing regimen of Claim 8 is "for administering paliperidone palmitate to a renally impaired psychiatric patient in need of treatment for schizophrenia, schizoaffective disorder, or schizophreniform disorder" and consists of (1) a loading dose in the deltoid muscle "of from about 75 mg-eq. of paliperidone" on day 1; (2) a second loading dose in the deltoid muscle "of from about 75 mg-eq. of paliperidone . . . on the 6^{th} to about 10^{th} day of treatment"; and (3) a maintenance dose in the deltoid or gluteal muscle "of about 25 mg-eq. to about 75 mg-eq. of paliperidone" a month (± 7 days) after the second loading dose. *Id.* cols. 32:66–33:20.

Claim 13 of the '906 Patent covers the "dosing regimen of claim 11 wherein the psychiatric patient is in need of treatment for of a psychotic disorder wherein the psychotic disorder is schizophrenia." *Id.* col. 33:50–52. The dosing regimen of Claim 11 is "for administering paliperidone palmitate to a renally impaired psychiatric patient in need of treatment for psychotic disorder" and consists of (1) a loading dose in the deltoid muscle "of from about 75 mg-eq. of paliperidone" on day 1; (2) a second loading dose in the deltoid muscle "of from about 75 mg-eq. of paliperidone . . . on the eighth day of treatment"; and (3) a maintenance dose in the deltoid or gluteal muscle "of about 25 mg-eq. to about 50 mg-eq. of paliperidone" one month (± 7 days) after

[46] The Invega Sustenna label states that Invega Sustenna "is not recommended in patients with moderate or severe renal impairment." PTX-105 at 6.

the second loading dose. *Id.* col. 33:28–47.[47]

The '906 Patent contains additional discussion of renal impairment beyond its claims. In the "Detailed Description" section, for instance, the Patent-in-Suit directs that "patients with renal impairment will have a higher total exposure to paliperidone after i.m. injections of paliperidone palmitate. For patients with renal impairment it would [be] desirable to adjust the loading doses to account for the increased exposure levels of patients with renal impairment." *Id.* col. 5:54–58. This section also instructs that "[f]or patients with mild renal impairment the loading doses should be reduced to 75 mg-eq. for the first two loading doses" and that "[f]or the purpose of this patent application renal function is estimated by glomerular filtration rate (GFR) usually measured by the creatinine clearance (best calculated from a 24-hour urine collection) . . . . Patients with mild renal impairment have a creatinine clearance of 50 to <80 mL/minute." *Id.* cols. 5:59–6:15.

3. Analysis

The Court finds that the '906 Patent sufficiently describes the claimed loading doses for renally impaired patients. A patent must include sufficient details such that a POSA could understand the subject invention and recognize that the inventor possessed it. *Ariad Pharm. Inc.*, 598 F.3d at 1351. However, this requirement does not necessarily mean that the specification of the patent must include every nuanced detail as "a patent need not teach, and preferably omits, what is well known in the art." *Falko-Gunter Falkner*, 448 F.3d at 1365 (quoting *Spectra-Physics, Inc. v. Coherent, Inc.*, 827 F.2d 1524, 1534 (Fed. Cir. 1987)). Here, Teva has failed to show by clear and convincing evidence that the Renal Impairment Claims lack adequate written description. *See Ariad Pharms., Inc.*, 598 F.3d at 1351 ("[T]he test for sufficiency is whether the disclosure of

[47] While Claims 20 and 21 (which generally describe the characteristics of the paliperidone palmitate formulation) are included in Teva's written description challenge as they refer back to the dosing regimens for patients with renal impairment, they are not independently analyzed by the parties.

the application relied upon reasonably conveys to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date.").

a) Relevant Testimony

Based on the testimony and evidence presented at trial, the Court finds that a POSA would have understood that the inventors of the '906 Patent had possession of the invention embodied in the Renal Impairment Claims as of the filing date of the '906 Patent. Experts for both parties in fact agreed that the '906 Patent instructs that paliperidone palmitate doses must be lowered when given to patients with renal impairment because paliperidone is cleared through the kidneys and renally impaired patients have reduced kidney function. *See* Trial Tr. (Kahn) at 116:1–3 ("It specifies to mild renal impairment, which wasn't in the other two, and that the loading dose should be reduced to 75 milligrams."); Trial Tr. (Kohler) at 1997:8–13 (agreeing that the '906 Patent states that "for patients with mild renal impairment, the loading doses should be reduced to 75-milligrams equivalent for the first two loading doses").

Further, both experts agreed that Invega Sustenna is not designed to be given to patients with moderate or severe renal impairment. *See* Trial Tr. (Kahn) at 105:12–15 ("**Q.** And then you may have said this, but for moderate and severe renal impairment, would a psychiatrist give Invega Sustenna to those patients? **A.** Well, it's not recommended, so I doubt it."); Trial Tr. (Kohler) at 1998:6–8 ("The way I read these specifications and the patent claims is that you do not administer paliperidone palmitate to people with moderate or severe renal impairment.").

Finally, the experts further agreed that the highest dose listed in the '906 Patent, 150 mg-eq., would be the upper limit for dosing any patient with renal impairment. *See* Trial Tr. (Kahn)[48]

[48] In Dr. Kahn's opening expert report, he wrote that "nothing in the '906 Patent indicates to a skilled artisan that the inventors were in possession of dosing regimens for administering paliperidone palmitate in schizophrenia patients with renal impairment in doses ranging from 75 mg eq. to infinity." Kahn Opening Expert Report at 14–15. The Court notes that Dr. Kahn's

at 145:12–14 ("I said, you know, the upper limit -- I am willing to accept that the upper limit is 150 milligrams."); Trial Tr. (Kohler) at 1935:7 (agreeing with Dr. Kahn that "the upper limit for the initiation doses for any patient is 150-milligram equivalents"). In addition, both experts testified that, at the time of the filing of the '906 Patent, it would have been well known to a POSA how to measure a patient's level of renal impairment. *See* Trial Tr. (Kahn) at 146:9–10 ("I mean, in general it can be done with a GFR. By assessing the GFR, yes."); Trial Tr. (Kohler) at 1936:17–19 ("Renal function is estimated by the glomerular filtration rate, or GFR, and which we can use the creatinine clearance as a proxy.").

Based on this testimony and the text of the '906 Patent, the Court finds that the Renal Impairment Claims are adequately described. The '906 Patent clearly conveys a dosing regimen for patients with renal impairment, supported by the specification which specifically discusses dosing for patients suffering from mild renal impairment. It would have been reasonably conveyed to a POSA that the maximum dose listed in the '906 Patent is 150 mg-eq. and that Invega Sustenna is not recommended for patients with moderate to severe renal impairment. As the written description requirement does not mandate that a patent expressly state all information currently known in the art, the Court finds the '906 Patent is not invalid.

b) Relevant Caselaw

The law is clear that written description must focus on whether a patent reasonably conveys possession of the claimed subject matter to those skilled in the art. *Ariad Pharms., Inc.*, 598 F.3d at 1351. The written description requirement is highly contextual and fact-dependent, taking into account the nature and scope of the claims, what is already known in the art, and the complexity of the invention. *See id*. ("[T]he level of detail required to satisfy the written description

written description testimony evolved to acknowledge that the '906 Patent contains an upper limit for dosing, as indicated above.

requirement varies depending on the nature and scope of the claims and on the complexity and predictability of the relevant technology."). The following cases are instructive.

The Court in *In re Wertheim*, 541 F.2d 257 (C.C.P.A. 1976), held that a patent's specification and what is well-known in the art must be read together when conducting a written description analysis. *Id.* at 265. Applying this holding, the court rejected a written description challenge over the claimed invention, finding that the patent sufficiently described the invention in light of its specific embodiments and what was known in the prior art. *Id.* at 264–65. Here, the Renal Impairment Claims set out a dosing regimen containing specific dosing instructions which are sufficiently described when combined with the information contained in the '906 Patent and known in the art that: the maximum dosage listed in the '906 Patent for any patient is 150 mg-eq., levels of renal impairment can be measured using standardized methods, and Invega Sustenna is not suitable for patients with moderate to severe renal impairment. As such, the Renal Impairment Claims are supported by adequate written description because "[i]t is not necessary that the application describe the claim limitations exactly . . . but only so clearly that persons of ordinary skill in the art will recognize from the disclosure that appellants invented processes including those limitations." *Id.* at 262.

Further, in *Nalpropion Pharmaceuticals, Inc. v. Actavis Laboratories FL, Inc.*, 934 F.3d 1344 (Fed. Cir. 2019), the Federal Circuit held that "[i]t is not necessary that the exact terms of a claim be used in *haec verba* in the specification." *Id.* at 1350. On this basis, the court rejected a written description challenge wherein the claim and the specification used different terms and methods to describe a process, finding the different language did not create a written description issue. *Id.* at 1351. As with the patent at issue in *Nalpropion*, the Court finds that the specification and the Renal Impairment Claims of the '906 Patent can be read and understood together despite

not using the exact same language. Accordingly, a "flexible, sensible interpretation" of the Patent-in-Suit shows that the inventors of the '906 Patent had possession of the invention embodied in the Renal Impairment Claims as of the filing date. *Nalpropion Pharms., Inc.*, 934 F. 3d at 1351; *see also Martek Biosciences Corp. v. Nutrinova, Inc.*, 579 F.3d 1363, 1371 (Fed. Cir. 2009) ("[A] patent claim is not necessarily invalid for lack of written description just because it is broader than the specific examples disclosed.").

The cases on which Defendant relies do not alter the Court's analysis. Each of these cases is factually distinguishable from this matter, or in fact supports the Court's finding and reaffirms that the proper written description inquiry is whether the '906 Patent reasonably conveys possession of the claimed subject matter to those skilled in the art.

Synthes USA, LLC v. Spinal Kinetics, Inc., 734 F.3d 1332 (Fed. Cir. 2013), essentially hinged on the meaning of a single word and how it was understood within a given field based on extensive evidence and testimony presented at trial. *Id.* at 1342. Here, as in *Synthes*, the Court makes its written description decision based upon evidence and testimony presented at trial. The evidence presented to the Court was clear that Invega Sustenna should not be used to treat patients with moderate or severe renal impairment (*see* Trial Tr. (Kahn) at 105:12–15; Trial Tr. (Kohler) at 1999:6–14) and confirmed that the Renal Impairment Claims convey possession of a dosing regimen for patients with mild renal impairment.

In *Pernix Ireland Pain DAC v. Alvogen Malta Operations Ltd.*, 323 F. Supp. 3d 566 (D. Del. 2018), the district court found the patents at issue invalid because "the invention is a method of treating pain that consists of administering a particular formulation to patients," but the patents failed to identify the class of formulations that will work and were drafted in functional terms. *Id.* at 625–26. Accordingly, the Court found that the patents "merely describe[] the problem to be

solved and claim[] all solutions to it." *Id*. Unlike in *Pernix*, the Renal Impairment Claims are not written in functional terms, but rather recite specific dose amounts to be used in a specific manner at specific times when treating a renally impaired psychiatric patient in need of treatment for schizophrenia or psychotic order. '906 Patent (DTX-1/PTX-1) cols. 32:67–34:47. Additionally, as noted above, Invega Sustenna is not recommended for patients with moderate or severe renal impairment, and the '906 Patent makes no reference to these types of renal impairment. In this factual context the dosing regimens for patients with renal impairment contained within the Renal Impairment Claims are a stark contrast to the claims at issue in *Pernix*.

Eli Lilly & Co. v. Perrigo Co., 202 F. Supp. 3d 918 (S.D. Ind. 2016) is also distinguishable from the present matter as the patent at issue in *Eli Lilly* contained a claim calling for a "at least one dermal penetration enhancer present in an amount of from 10 to 10,000[%] based on the weight of the testosterone," and there was inadequate guidance from the patent specification or examples that could help narrow the entire expansive range of 10–10,000%. *Id.* at 929, 996–97. Here, the specification of the '906 Patent contains multiple embodiments and discussions of the renal impairment claims, specifically discussing how to utilize the dosing regimen (which recites specific dose amounts, sites of injection, and dose timing) for patients with mild renal impairment and how to calculate mild renal impairment. *Id.* col. 3:27–56, col. 5:53–6:14.

Thus, the Court finds that the Renal Impairment Claims, when read in context of what is described in the specification, and what is detailed in the embodiments, reasonably convey to those skilled in the art possession of the claimed invention. Based on the testimony and evidence presented at trial, as well as the arguments presented to the Court at closing arguments and in the parties' papers, the Court finds that Teva has failed to show by clear and convincing evidence that the Renal Impairment Claims fail based on a lack of written description. Next, the Court addresses

Teva's indefiniteness challenge.

C. Indefiniteness (35 U.S.C. § 112)

"[A] patent is invalid for indefiniteness if its claims, read in light of the specification delineating the patent, and the prosecution history, fail to inform, with reasonable certainty, those skilled in the art about the scope of the invention." *Nautilus, Inc. v. Biosig Instruments, Inc.*, 572 U.S. 898, 901 (2014). Indefiniteness is a question of law, which may rely on subsidiary determinations of underlying facts. *Akzo Nobel Coatings, Inc. v. Dow Chem. Co.*, 811 F.3d 1334, 1343 (Fed. Cir. 2016). A patent is presumed to be valid; the challenger bears the burden of establishing invalidity by clear and convincing evidence. 35 U.S.C. § 282(a); *Microsoft Corp. v. i4i Ltd. P'ship*, 564 U.S. 91, 95 (2011).

Defendant argues that the Patent-in-Suit is invalid as indefinite for two reasons. First, Defendant argues that Claims 20 and 21 fail to properly characterize the claimed d50 range given that d50 can be measured and expressed in a number of different ways. Def. Br. at 70. Second, Defendant contends that Claims 10, 20, and 21 fail to properly characterize the term "aqueous nanoparticle suspension" which lacks a typical meaning in the art. *Id.* at 74. Plaintiffs argue that Claims 20 and 21 are not indefinite because Teva failed to show that different methods or expressions of measurement lead to meaningfully different results. Pls. Br. at 65. Plaintiffs further contend that Claims 10, 20, and 21 are not indefinite because the '906 Patent defines the term aqueous nanoparticle suspension and makes clear the d50 ranges that encompass a nanoparticle. *Id.* at 68. In support of their arguments, the parties rely on the testimony of the following witnesses: Defendant's expert Lawrence Block, Ph.D.,[49] and Plaintiffs' expert Dr. Sinko

[49] Defendant's expert Lawrence Block, Ph.D., is a Professor Emeritus of Pharmaceutics at the School of Pharmacy and Graduate School of Pharmaceutical Sciences at Duquesne University. Final Pretrial Order at 42. Dr. Block is recognized as a leader in the field of pharmaceutics and is a Fellow of both the American Association of Pharmaceutical Scientists and the American

(introduced above). For the reasons set forth below, the Court finds that Defendant has failed to prove invalidity based on indefiniteness by clear and convincing evidence, and therefore the Patent-in-Suit is not invalid under 35 U.S.C. § 112.

1. Overview of the Parties' Positions

a) d50 Indefiniteness

Defendant argues that Claims 20 and 21 are indefinite because although they require "an average particle size (d50) of from about 1600 nm to about 900 nm," this requirement fails to properly limit the claims due to numerous variations that affect particle size measurements. Def. Br. at 70. Defendant notes that the paliperidone palmitate particles described in the '906 Patent are asymmetrical and their size is reported as the diameter of a hypothetical equivalent sphere which can be measured using different techniques and expressed in different ways. *Id.* at 70–71. Defendant also notes that the type of instrument used to make measurements, and the conditions under which particles are measured, can influence measurements. *Id.* at 71.

Plaintiffs respond that "a claim term is not indefinite for failure to specify which method should be used to measure a quantity unless different methods lead to significantly different results, and there is no evidence of that here." Pls. Br. at 65. Plaintiffs further argue that different measurements of particle size taken at different times are equally correct, that instrument error accounts for the only meaningful discrepancy in particle size measurement discussed at trial, and that no ordinary scientist would have difficulty measuring the particle size of paliperidone palmitate suspensions, also noting that scientists at the FDA and USPTO did not have any difficulty taking particle size measurements during the relevant agency proceedings. *Id.* at 66–68.

Pharmacists Association - Academy for Pharmaceutical Research and Science. *Id.* Dr. Block has authored or co-authored over 120 publications and his research interests include excipient technology, rheology, drug and cosmetic delivery systems, pharmaceutical engineering, biopharmaceutics, and pharmacokinetics. *Id.* at 42–43.

b) Aqueous Nanoparticle Suspension Indefiniteness

Defendant argues that Claims 10, 20, and 21 are "invalid for failing to define the bounds of the term aqueous nanoparticle suspension." Def. Br. at 74 (internal quotation marks omitted). Defendant maintains that this term has no typical meaning in the art, that no definite bounds of particle size are provided, and that the '906 Patent incorporates "suitable aqueous depot formulations" from the '843 Patent that exceed the particle sizes listed in the '906 Patent, making it impossible for a POSA to determine with reasonable certainty whether a formulation is a nanoparticle suspension or not. *Id.* at 74–75.[50]

Plaintiffs argue that the '906 Patent adequately defines the term aqueous nanoparticle suspension and "makes clear that suspensions having an average particle size d50 within the ranges disclosed in the patent's specification and claims qualify as nanoparticle suspensions." Pls. Br. at 68 (internal quotation marks omitted). Plaintiffs also stress that "[e]ven if an ordinarily skilled person might be interested in further information about particle size distribution for other purposes, they would have no difficulty determining the 'scope of the invention' with reasonable certainty," which is all that is required to render a claim definite. *Id.* (citing *Nautilus, Inc.*, 572 U.S. at 901).

2. The Claims Relevant to Indefiniteness

Claim 10 of the '906 Patent covers the "dosing regimen of claim 8 wherein the sustained release formulation is an aqueous nanoparticle suspension." '906 Patent (DTX-1/PTX-1) col. 33:26–27. The dosing regimen of Claim 8 is "for administering paliperidone palmitate to a renally impaired psychiatric patient in need of treatment for schizophrenia, schizoaffective disorder, or

[50] To the extent Teva also argues that the term aqueous nanoparticle suspension is indefinite because the '906 Patent incorporates the '843 Patent and '544 Patent into its disclosure, Teva has not supported this argument with persuasive testimony or evidence presented at trial. The Court also notes that "nanoparticle" does not appear in the '843 Patent and finds that the incorporation by reference of these patents does not render the term aqueous nanoparticle suspension indefinite for the reasons discussed below.

schizophreniform disorder" and consists of (1) a loading dose in the deltoid muscle "of from about 75 mg-eq. of paliperidone" on day 1; (2) a second loading dose in the deltoid muscle "of from about 75 mg-eq. of paliperidone . . . on the 6th to about 10th day of treatment"; and (3) a maintenance dose in the deltoid or gluteal muscle "of about 25 mg-eq. to about 75 mg-eq. of paliperidone" a month (± 7 days) after the second loading dose. *Id.* cols. 32:66–33:20.

Claim 20 of the '906 Patent covers the "dosage regimen of claim 19 wherein the buffering agents contained in the aqueous nanoparticle suspension are citric acid monohydrate, disodium hydrogen phosphate anhydrous, sodium dihydrogen phosphate monohydrate, sodium hydroxide." *Id.* col. 34:44–48. Claim 19 of the '906 Patent provides details on the aqueous nanoparticle suspension to be used as a sustained release depot formulation in the dosing regimens of Claims 1, 4, 8, or 11. *Id.* col. 34:32–34. Specifically, it instructs that the aqueous nanoparticle suspension should consist of: (1) 156 mg/ml of paliperidone palmitate "having an average particle size (d50) of from about 1600 nm to about 900 nm"; (2) 12 mg/ml of polysorbate 20; (3) one or more buffering agents sufficient to give the composition a pH of 8.5; (4) 30 mg/ml of the suspending agent polyethylene glycol 4000; and (5) "water q.s. ad 100%." *Id.* col. 34:34–43.

Claim 21 of the '906 Patent covers the "dosage regimen of claim 19 wherein the pH of the aqueous nanoparticle suspension is in the range of pH 7 to 7.5." *Id.* col. 34:49–51.

3. Analysis

a) d50 Indefiniteness

The Court finds that Claims 20 and 21[51] are not invalid for indefiniteness as "the mere possibility of different results from different measurement techniques does not render a claim indefinite." *Ball Metal Beverage Container Corp. v. Crown Packaging Tech., Inc.*, 838 F. App'x

[51] Claim 10 will be discussed in connection with the aqueous nanoparticle suspension indefiniteness analysis below.

538, 542 (Fed. Cir. 2020) (internal citations and quotation marks omitted). Teva has failed to provide clear and convincing evidence that possible variations in d50 measurement methodology and procedure would lead to materially different results such that Claims 20 and 21 "fail to inform, with reasonable certainty, those skilled in the art about the scope of the invention." *Nautilus, Inc.*, 572 U.S. at 901.

i. Relevant Testimony

The testimony of Defendant's expert, Dr. Block, and Plaintiffs' expert, Dr. Sinko, is largely consistent on a number of key issues relevant to this Court's analysis. Both experts agree that a POSA would be able to use different methods to measure a particle size of d50. *See* Trial Tr. (Block) at 589:6–13 (testifying that the specification "tells one to measure [d50] by art-known conventional techniques," and "gives examples of art-known conventional techniques," such as "Sedimentation field flow fractionation, photon correlation spectroscopy and disk centrifugation"); Trial Tr. (Sinko) at 1554:1–3 ("[T]here were several methods for measuring. And this is just some of the machines that were listed in those relevant sections that I discussed. These are a few examples.").

Both experts further agree that that using different methods, tools, or expressions of measuring d50 can lead to the same or materially similar results, and that different d50 measurements of the same particle size can all be "correct" measurements that vary because of the conditions under which the particle was measured. *See* Trial Tr. (Block) at 613:13–16 ("**Q.** So we've talked about a lot of different techniques this morning and this afternoon. Is there one technique that's more correct than others? **A.** No."); *Id.* (Block) 630:18–25 ("**Q.** Sure. Whether or not there are significant differences between number-weighted, volume-weighted and intensity-weighted d50 measurements would depend on various factors, right? **A.** Yes. **Q.** And

the differences may or may not be significant, depending upon those factors, right? **A.** That's true."); Trial Tr. (Sinko) at 2194:16–20 ("**Q.** And if you use all those different methods, you'd come up with a different diameter, potentially, right? **A.** Maybe. **Q.** Maybe you would, right? **A.** And maybe you wouldn't."); *Id.* (Sinko) 2195:19–2196:2 ("**Q.** You agree, Doctor, that the '906 patent does not limit the d50 value expressly to any particular type of diameter measurement, right? **A.** It states a d50, that's true. But as we saw from the data from, you know, from Janssen, from Teva, you know, using multiple methods, you get the same answer. . . . And they use different methods with different diameters, and they get the same answer.").

Finally, both experts agree that throughout the development of Invega Sustenna, the prosecution of the Patent, and the development of Teva's ANDA, there was no apparent confusion over how to measure or express d50 that cannot be explained by artificial error. *See* Trial Tr. (Block) at 650:8–11 ("**Q.** And Teva was able to determine the d50 value for its paliperidone palmitate suspension and report that value to the FDA, right? **A.** Apparently."); Trial Tr. (Sinko) at 1563:7–9 ("**Q.** Was there any suggestion that either the FDA or Teva had any difficulty understanding a d50 particle size distribution? **A.** No, there was not.").

The relevant disagreement here comes almost entirely from counsel, as they disagree over the legal significance of the largely congruent testimony of Dr. Block and Dr. Sinko. A review of the relevant caselaw cited by the parties, however, confirms that any asserted differences in measuring and expressing d50 particle size present in this matter do not render Claims 20 and 21 invalid because a POSA would understand, "with reasonable certainty," the scope of the d50 particle measurement within Claims 20 and 21.

ii. *Relevant Caselaw*

A review of the relevant caselaw demonstrates that the differing methods of measuring and

representing d50 particle size must lead to meaningfully different results in order to render Claims 20 and 21 indefinite. In *PPG Industries, Inc. v. Guardian Industries Corp.*, 75 F.3d 1558 (Fed. Cir. 1996), the party challenging patent validity argued that the claims at issue were indefinite because "the inventors failed to state the method they used to measure the ultraviolet transmittance of the invention." *PPG Indus., Inc.*, 75 F.3d at 1562. The Federal Circuit rejected this argument, finding that the evidence presented "established that, setting aside the equipment error that plagued PPG's testing procedures, all of the conventional methods of testing ultraviolet transmittance produce essentially identical results." *Id.* at 1563.[52] Similarly, in *Ethicon Endo-Surgery, Inc. v. Covidien, Inc.*, 796 F.3d 1312 (Fed. Cir. 2015), the Federal Circuit found that slight variations in measurements taken through different methods did not render the claims at issue indefinite because they were "simply due to natural variances in real-world testing conditions." *Id.* at 1319–20, 1322. In *Takeda Pharmaceutical Co., Ltd. v. Zydus Pharmaceuticals USA, Inc.*, 743 F.3d 1359 (Fed. Cir. 2014), the Federal Circuit stressed that "there is no evidence that the differences between these techniques are in fact significant; there was evidence before the trial court that although the results may be different, there is a high degree of correlation for the results between the two techniques, . . . indeed, there was no evidence in this case that different measurement techniques in fact produced significantly different results for the same sample." *Id.* at 1367 (internal citations and

[52] *PPG Industries* is also instructive because in the present case Teva seeks to place great weight on an outlier measurement taken with a defective device. Def. Br. at 72 (noting differences in measurements Janssen obtained using "Coulter counter" and "Mastersizer"). As *PPG Industries* instructs, the Court does not find that this outlier measurement renders the claims at issue indefinite because it has been adequately explained (with no persuasive rebuttal) as an equipment defect. *See* Trial Tr. (Sinko) at 1558:4–9 ("So basically using three different methods they came up with, in essence, the same particle size distribution, and therefore they could conclude that that Coulter and the artifact that they thought existed was definitely an artifact or an artificial result. And so they could rely on their laser diffraction original method, the Malvern Mastersizer."); Trial Tr. (Block) at 662:6–17 (testifying that Janssen found artificial differences between the Coulter and the Malvern device measurements).

quotation marks omitted). Based on this evidence, the Federal Circuit held that "[a]ny theoretical minor differences between the two techniques are therefore insufficient to render the patent invalid." *Id.*

Cases that find patents invalid based upon different methods of measurement crucially contain evidence that the different methods are likely to lead to significantly different results. In *Dow Chemical Co. v. Nova Chemicals Corp. (Canada)*, 803 F.3d 620 (Fed. Cir. 2015), the Federal Circuit found the claims at issue invalid as "[t]here is no question that each of these four methods may produce different results, i.e., a different slope" based on Dow's expert testimony which conceded that "the 10% secant tangent method, the final slope method, the most linear method, and the method he invented could produce different results. In comparison to the three other methods, [the Dow expert]'s method would produce a higher value." *Id.* at 633–635. In *Teva Pharmaceuticals USA, Inc. v. Sandoz, Inc.*, 789 F.3d 1335 (Fed. Cir. 2015), the indefiniteness analysis hinged on the term "molecular weight" which can be measured and expressed in multiple forms. *Id.* at 1338. The Federal Circuit found these different forms of molecular weight rendered the patent at issue invalid as "[t]he parties agree that 'molecular weight' could refer to [peak average molecular weight, number average molecular weight, or weight average molecular weight]. And they agree that each of these measures is calculated in a different way and would typically yield a different result for a given polymer sample." *Id.* at 1341, 1345. *Otsuka Pharmaceutical Company, Ltd. v. Torrent Pharmaceuticals, Ltd., Inc.*, 151 F. Supp. 3d 525 (D.N.J. 2015), involved the question of whether the term "mean particle size" was indefinite "because it's amenable to multiple meanings." *Id.* at 544. In finding this term indefinite, the district court first noted that "Otsuka readily acknowledges the susceptibility of 'mean particle size' to multiple measurements, each of which could yield varied results," and found that the record showed a lack

of uniform understanding of the term in the relevant scientific community, and that the patent at issue provided "no information from which to divine, with reasonable certainty, the appropriate measure of the 'mean.'" *Id.* at 546–48.

Here, the '906 Patent does discuss methods of measuring d50 and does contain examples wherein those methods are utilized. *See* Trial Tr. (Block) at 637:2–11 ("**Q.** The patent reports a particle size distribution was measured by laser diffraction, correct? **A.** Yes. **Q.** So you would agree that a person of skill in the art reading the patent would know that they could measure particle size by laser diffraction, right? **A.** Yes. **Q.** And if you measure particle size by laser diffraction, you typically get a volume-weighted measure of d50, right? **A.** That's my understanding."). Additionally, the evidence and testimony admitted during the bench trial showed that the different methods of measuring and expressing d50 were likely to produce substantially similar values. *See* Trial Tr. (Block) at 651:25–652:7 [redacted]; Trial Tr. (Sinko) at 2196:5–10 ("I don't think it needs to be. I mean, that's – everyone uses the methods. And they know that the software that every manufacturer uses for their different methods normalizes for all this because otherwise, no one would be able to rely on it. And everyone does rely on it. Teva relies on it. Janssen relies on it. My lab relies on it."). As the '906 Patent provides examples of how to measure d50 particle size and different methods or expressions of measurement lead to essentially identical values, the differing methods or expressions would have no effect on a POSA's ability to understand the scope of the claims with reasonable certainty. Additionally, the Court notes that both experts testified at trial that throughout the relevant agency proceedings there were no issues with measuring d50,

providing further evidence to support the finding that differing methods or expressions of d50 do not render Claims 20 and 21 indefinite. *See* Trial Tr. (Block) at 650:8–11; Trial Tr. (Sinko) at 1563:7–9.

Based on all of the evidence and testimony presented at trial, the Court finds that Teva has failed to show by clear and convincing evidence that the different methods or expressions of d50 particle size render Claims 20 and 21 invalid.

b) Aqueous Nanoparticle Suspension Indefiniteness

The Court also finds that Claims 10, 20, and 21 are not invalid for indefiniteness based on their utilization of the term "aqueous nanoparticle suspension." That term is defined with reasonable certainty.

i. Relevant Testimony

At trial, Dr. Block, Teva's expert, agreed that the '906 Patent describes "characteristics of the nanoparticle suspension," such as the range of 1600 nanometers to 400 nanometers for particle size d50, but maintained that the term is indefinite because "there could be particles potentially outside that range on the upper end and some particles below that range." Trial Tr. (Block) at 670:10–14; 672:8–18. Dr. Sinko, Janssen's expert, disagreed with Dr. Block and stated that the '906 Patent adequately defines the term because "it says, an aqueous formulation would preferably be a nanoparticle suspension of wherein the nanoparticles would fit in average sizes of less than 2000 nanometers to about 100 nanometers. And then it goes on and on. But basically, you know, it defines what an aqueous nanoparticle suspension is." Trial Tr. (Sinko) at 1560:24–1561:4.

The Court agrees with Dr. Sinko that the term "aqueous nanoparticle suspension" is defined with reasonable certainty in the '906 Patent and rejects the arguments proffered by Teva that this definition is lacking.

ii. Relevant Caselaw

In *Vapor Point LLC v. Moorhead*, No. 11-4639, 2013 WL 11275459 (S.D. Tex. Dec. 18, 2013), the district court found the term "micro-sized particles" not indefinite, noting that "[a]n issued claim is presumed valid." *Vapor Point LLC*, 2013 WL 11275459, at *17 (internal citations and quotation marks omitted). The *Vapor Point* plaintiffs argued that the term micro-sized particles was indefinite because it was used in a manner contrary to its ordinary meaning, but the court rejected that argument as it found that the "specification communicates a deliberate and clear preference for an alternative definition." *Id.* The court also noted that "close questions of indefiniteness" are resolved in favor of the valid patent. *Id.* Finally, the court found "no clear conflict" in the patent's specification that "micro-sized particles may vary in range between 5–500 microns, although smaller and larger particles may also be used with embodiments described herein." *Id.*

These holdings make clear that the '906 Patent is not indefinite based on the term aqueous nanoparticle suspension. As in *Vapor Point*, the '906 Patent provides a clear definition of the term aqueous nanoparticle suspension such that there does not need to be an ordinary meaning of the term. Specifically, the '906 Patent states that the aqueous nanoparticle suspension would preferably have nanoparticles of an average size of less than 2000 nm to about 100 nm, and provides further details on the preferred d50 and d90 measurements for nanoparticles. '906 Patent (DTX-1/PTX-1) col. 7:24–32. In addition, *Vapor Point* instructs that the '906 Patent's failure to define what is not an aqueous nanoparticle suspension does not render it indefinite, as the court in that case found the patent's reference to "smaller and larger particles" did not render the claims at issue indefinite.

For all of the reasons discussed at length above, the Court finds Teva has failed to show by clear and convincing evidence that Claims 10, 20, and 21 fail as indefinite based on the testimony and evidence presented at trial.

D. Rule 52(c) Motions

During the bench trial, both parties made motions for judgment on partial findings pursuant to Federal Rule of Civil Procedure 52(c). ECF Nos. 138, 150. Rule 52(c) reads:

> If a party has been fully heard on an issue during a nonjury trial and the court finds against the party on that issue, the court may enter judgment against the party on a claim or defense that, under the controlling law, can be maintained or defeated only with a favorable finding on that issue. The court may, however, decline to render any judgment until the close of the evidence. A judgment on partial findings must be supported by findings of fact and conclusions of law as required by Rule 52(a).

Fed. R. Civ. P. 52(c). Thus, Rule 52(c) permits a judge to enter judgment as a matter of law on partial findings once "a party has been fully heard on an issue." *Id.* "To grant a [motion for judgment as a matter of law] under Rule 52(c), a district judge must weigh the evidence and resolve credibility." *Yamanouchi Pharm. Co. v. Danbury Pharmacal, Inc.*, 231 F.3d 1339, 1343 (Fed. Cir. 2000). "A judgment on partial findings is made after the court has heard all the evidence bearing on the crucial issue of fact." Fed. R. Civ. P. 52(c) advisory committee's note to 1991 amendment.

Consistent with the terms of Rule 52(c), the Court exercised its discretion to reserve judgment on the motions during trial. Fed. R. Civ. P. 52(c) ("The court may, however, decline to render any judgment until the close of the evidence."). The Court now concludes that the best course of action is to render a judgment based on all of the evidence, testimony, and applicable law. Accordingly, the Rule 52(c) motions (ECF Nos. 138, 150) are denied.

E. Motion to Correct Inventorship (35 U.S.C. § 256)

Along with its post-trial submissions, Plaintiffs also filed a renewed motion (in lieu of a

previously withdrawn motion)[53] "for the entry of an Order pursuant to 35 U.S.C. § 256(b) directing the United States Patent and Trademark Office [] to issue a certificate adding Drs. Srihari Gopal and Mahesh Samtani as inventors of U.S. Patent No. 9,439,906." ECF No. 166 at 1.[54] Plaintiffs rely on the trial record as well their post-trial briefs, proposed findings of fact, and proposed conclusions of law in support of this motion. *Id.* at 1–2. Plaintiffs argue that Drs. Gopal and Samtani should be added as inventors of the '906 Patent based on trial testimony describing their substantial contributions to the claimed invention and corroborating contemporaneous evidence introduced and admitted at trial. Pls. Br. at 72–73. Teva did not file a separate brief in opposition to Plaintiffs' renewed motion to correct inventorship, but instead argued against the motion in its post-trial submissions. *See* Def. Br. at 42–43; Def. Reply Br. at 42–47. Teva contends that Janssen has improperly changed its position on inventorship insofar as it asserted that there were four additional inventors of the '906 Patent in the Final Pretrial Order, but now only seeks to add Drs. Gopal and Samtani. Def. Br. at 42–43. Teva also argues that the testimony presented at trial establishes that there were numerous additional individuals who made contributions to the '906 Patent and could be considered inventors, that the entire inventive entity must be correct, and that Janssen failed to provide corroborating evidence confirming that Drs. Gopal and Samtani should be added as inventors. *Id.*; Def. Reply Br. at 43–47.

District courts may order the correction of patent inventorship by the USPTO "on notice

[53] Plaintiffs initially filed a motion to amend/correct inventorship pursuant to 35 U.S.C. § 256(b) on June 17, 2020. ECF No. 91. After full briefing on that motion (ECF Nos. 91-2, 115, 118) and oral argument (ECF No. 127), that motion was withdrawn by Plaintiffs who indicated they would file a renewed motion after trial to conform with the evidence presented to the Court. *See* ECF No. 127. Janssen now renews the motion as to Drs. Gopal and Samtani. ECF No. 166; PFOF ¶ 296.

[54] The Court also notes that in 2017, Janssen directly filed an application with the USPTO asking it to correct inventorship of the '906 Patent, but the USPTO has not taken action with respect to that application. Final Pretrial Order at 12.

and hearing of all parties concerned." 35 U.S.C. § 256(b). The concerned parties are "named inventors, omitted inventors, and assignees." *See Nichols Inst. Diagnostics, Inc. v. Scantibodies Clinical Lab'y, Inc.*, 218 F. Supp. 2d 1243, 1250 (S.D. Cal. 2002). 35 U.S.C. § 116(a) provides the standard for joint inventorship:

> When an invention is made by two or more persons jointly, they shall apply for patent jointly and each make the required oath, except as otherwise provided in this title. Inventors may apply for a patent jointly even though (1) they did not physically work together or at the same time, (2) each did not make the same type or amount of contribution, or (3) each did not make a contribution to the subject matter of every claim of the patent.

"[A] joint invention is simply the product of a collaboration between two or more persons working together to solve the problem addressed." *Fina Oil & Chem. Co. v. Ewen*, 123 F.3d 1466, 1473 (Fed. Cir. 1997) (citing *Burroughs Wellcome Co. v. Barr Lab'ys, Inc.*, 40 F.3d 1223, 1227 (Fed. Cir. 1994)). To be a joint inventor, one must:

> (1) contribute in some significant manner to the conception or reduction to practice of the invention, (2) make a contribution to the claimed invention that is not insignificant in quality, when that contribution is measured against the dimension of the full invention, and (3) do more than merely explain to the real inventors well-known concepts and/or the current state of the art.

Pannu v. Iolab Corp., 155 F.3d 1344, 1351 (Fed. Cir. 1998). "Because the issuance of a patent creates a presumption that the named inventors are the true and only inventors, the burden of showing . . . nonjoinder of inventors is a heavy one and must be proved by clear and convincing evidence." *Falana v. Kent State Univ.*, 669 F.3d 1349, 1356 (Fed. Cir. 2012) (internal citation omitted). To meet the clear and convincing evidence standard, putative joint inventors must provide some corroborating evidence instead of relying solely on their own testimony. *Symantec Corp. v. Comput. Assocs. Int'l, Inc.*, 522 F.3d 1279, 1295 (Fed. Cir. 2008). This requirement for corroboration "addresses the concern that a party claiming inventorship might be tempted to

describe his actions in an unjustifiably self-serving manner in order to obtain a patent." *Chen v. Bouchard*, 347 F.3d 1299, 1309 (Fed. Cir. 2003). As such, the corroboration requirement only applies to a putative joint inventor's testimony; documentary evidence does not need corroboration before a court may consider it. *Price v. Symsek*, 988 F.2d 1187, 1195 (Fed. Cir. 1993).

As an initial matter, there are numerous cases holding that "alleged infringers have no innate right to participate in correction-of-inventorship proceedings, whether before the USPTO or a court on the complaint of a party to a patent." *Cobra Int'l, Inc. v. BCNY Int'l, Inc.*, No. 05-61225, 2014 WL 11321379, at *3 (S.D. Fla. Dec. 10, 2014); *see also Nichols Inst. Diagnostics, Inc.*, 218 F. Supp. 2d at 1250 ("An alleged infringer is not a necessary party to a motion for correction under § 256."). Nonetheless, Teva functionally raises arguments on behalf of other potential omitted inventors and maintains that the Court cannot correct the '906 Patent by only adding two omitted inventors when Janssen previously indicated there were four. Against the backdrop of the caselaw discussed above defining and limiting the interested parties to correction of inventorship proceedings pursuant to 35 U.S.C. § 256, the Court notes that Teva has now separately sought leave to amend its affirmative defenses to assert that the '906 Patent is invalid due to incorrect inventorship.

The Court finds more than adequate support in the record to confirm that Drs. Gopal and Samtani should be added as inventors of the '906 Patent.[55] At trial, Dr. Gopal testified credibly about his contributions to the '906 Patent, describing how he revised the dosing regimens,

[55] Janssen asserts the correction of inventorship is rather straightforward because the named inventors, patent assignee, and proposed inventors to be added all agree that inventorship of the '906 Patent should be corrected to add Drs. Gopal and Samtani. *See* Pls. Br. at 71 n.10 ("All concerned parties have waived their right to a hearing and/or participated in a trial on the subject matter of this motion, and they have consented to adding Drs. Gopal and Samtani as inventors of the 906 Patent."). Given the evidence and testimony presented at trial on this issue, however, the Court reviews the substance of the motion to correct inventorship in this Opinion.

examined results of the failed PSY-3002 study, and proposed the claimed dosing regimen. Trial Tr. (Gopal) at 1071:5–16 ("**Q.** Now, did you play a role in selecting the dosing regimen for the new trials? **A.** Yes, I did. **Q.** And what was your role? **A.** So my role was from the perspective of a physician and a clinician treating patients. So we would work closely with the modelers to tell them what was realistic, what potential scenarios to come up with, because they didn't have clinical training by background. So we would tell them what different doses to study, what injection sites, what time periods, and other factors that helped adjust the model."); *id.* at 1089:8–12 (discussing his analysis of results of failed PSY-3002 study: "So I was looking to try to figure out what went wrong in the study because a lot of people were asking me in senior management. So based on my looking at the data, these are the four points that I thought were potentially responsible for it.").

This testimony was corroborated by contemporaneous documents which were admitted into evidence. *See, e.g.*, PTX-235 at 3–4 (PowerPoint presentation created by Dr. Gopal in March 2007 titled "R092670-PSY-3007 Protocol Overview" which instructed investigators running clinical trials on study protocol); PTX-253 at 1 (email from Dr. Gopal regarding results of PSY-3002 study and discussing potential explanations for unexpected failure); PTX-256 at 1 (May 29, 2007 letter to investigators regarding temporary halt of PSY-3006 and PSY-3007 studies as Dr. Gopal and his team considered how to modify these studies in light of PSY-3002 results); PTX-263 at 9–10 (internal Janssen presentation that Dr. Gopal helped prepare, dated June 7, 2007, titled "Paliperidone Palmitate PSY-3002 Results & Implications for PSY-3006").

Dr. Samtani also testified with credibility about his contributions to the '906 Patent in the form of developing dosing windows for claims 2, 10, 13, 20, and 21, and developing the renal impairment dosing regimen. Trial Tr. (Samtani) at 1345:18–1346:8 ("**Q.** I understand you're not

a lawyer, but can you explain to the best of your ability what your significant contributions were to the '906 patent? **A.** So there are two distinct contributions that I can remember. The first one is the development of a dosing recommendation for psychiatric patients who also have mild renal impairment. So this particular dosing recommendation was designed only on the basis of modeling and simulation. And the other piece that I can remember is the designing of dosing windows around the regularly scheduled monthly maintenance injection and also a dosing window around the Day 8 loading dose for paliperidone palmitate. And so it is these dosing recommendations that are contributions that I can recollect are my contributions, among others, to this particular patent."); *id.* at 1349:5–11 (discussing PTX-251, a PowerPoint presentation given in April 2007, and stating, "So I had been working on this project for about two months, and at this point I had made a couple of major breakthroughs that were important findings that I was able to incorporate into the population PK models. And it was this update that I wanted to give to An Vermeulen, and this presentation was prepared as a project update for An Vermeulen in April of 2007.").

This testimony was also corroborated by contemporaneous documents described at trial and admitted into evidence. *See, e.g.*, PTX-251 at 19–20, 27 (presentation authored by Dr. Samtani dated April 27, 2007, titled: "AM&S Application: POP-PK Paliperidone Palmitate" discussing major updates developed through use of deconvolution analysis and the Hirano concept); PTX-278A at 35–36, 118–19 (draft population pharmacokinetic report from August 3, 2007, titled, "Clinical Pharmacology Advanced PK/PD Modeling and Simulation - Population Pharmacokinetic Analysis - R092760 (Paliperidone Palmitate)," which discussed comparisons of initiation regimes and documented that 150/100 mg-eq. day 1/day 8 dosing regimen is optimal); PTX-288 (final report submitted to FDA as part of Janssen's New Drug Application submission in Fall 2007 that included Dr. Samtani's modeling and findings); PTX-294A (PowerPoint sent by

Dr. Samtani to Janssen team in October 2007 summarizing population pharmacokinetic modeling and simulation). Accordingly, the Court finds that based on the testimony and evidence presented at trial, there is clear and convincing evidence that Drs. Gopal and Samtani should be added as inventors of the '906 Patent.[56]

F. Teva's Motion to Amend the Pleading

On July 7, 2021, Teva filed a motion to amend pursuant to Federal Rule of Civil Procedure 15(b)(2), asking the Court to deem its pleadings amended with a count for patent invalidity due to incorrect inventorship under 35 U.S.C. § 102(f), and to enter judgment in its favor on that claim. ECF No. 244. In its brief in support (ECF No. 245), Teva argues that Janssen both "expressly consented to trying the issue of inventorship" and conceded that the inventive entity of the '906 Patent is incorrect by seeking an order to correct inventorship under 35 U.S.C. § 256. *Id.* at 2–3. Teva makes a number of arguments in support of its motion. Teva argues that Janssen did not meet its burden under section 256 to add Drs. Gopal and Samtani as inventors of the '906 Patent. *Id.* at 4. In connection with this argument, Teva asserts that even adding Drs. Gopal and Samtani as inventors does not properly correct inventorship because Janssen previously indicated (in its now withdrawn pretrial motion) that there were four inventors to be added to the '906 Patent. *Id.* at 5–6. Teva also contends that Janssen did not offer any testimony or evidence as to Dr. Lewyn-Briscoe or Dr. Kusumakar despite previously indicating that they are also inventors of the '906 Patent. *Id.* Additionally, Teva argues that the record evidence presented at trial demonstrates that tens of people inside and outside Janssen contributed to the '906 Patent and that these people

[56] Teva also argues that Dr. Gopal at one point pushed for a higher second loading dose and only "acquiesced" to the dosing regimen in Claim 2. Def. Reply Br. at 45. This argument misses the focus of joint inventorship analysis, and fails to acknowledge the difficult and fluid process that Janssen went through in developing Invega Sustenna. Teva's arguments regarding Dr. Samtani's modeling efforts (*id.* at 46) similarly miss the mark.

should also be named as inventors. *Id.* at 4–5.

Janssen filed its brief in opposition on August 2, 2021. ECF No. 252. Janssen argues that Teva cannot assert a section 102(f) defense because it did not raise such a defense in its invalidity contentions as required by Local Patent Rule 3.3 and that Teva waived this argument by failing to include it in the Final Pretrial Order, raise it at trial, or brief the issue post-trial. *Id.* at 13–15. Janssen further argues that it did not consent to trying a section 102(f) defense, that no section 102(f) defense was implicitly tried, and that it would be greatly prejudiced if such a defense were introduced into the case at this time. *Id.* at 16–18. Janssen also asserts that there is no trial evidence to support a section 102(f) defense and that Teva has the burden of proof on this issue. *Id.* at 19–20. Finally, Janssen argues that even if the Court were to reach the merits of the section 102(f) invalidity challenge, the '906 Patent would not be rendered invalid under any potential scenario. *Id.* at 20–23.

Teva filed its reply in support on August 9, 2021. ECF No. 258. Echoing its original arguments, Teva maintains that Janssen placed inventorship at issue during trial, Janssen failed to provide evidence showing that Drs. Gopal and Samtani should be added as inventors of the '906 Patent, and that Teva has carried its burden of establishing invalidity by showing that inventorship of the '906 Patent is incorrect. *Id.* at 2–4.[57]

Rule 15(b)(2) allows for amendment of a complaint during or after trial when a claim not included in the complaint is tried by express or implied consent. *Swiatek v. Bemis Co.*, 542 F. App'x 183, 188 (3d Cir. 2013). It is difficult to find that Janssen expressly consented to Teva

[57] While Teva attempts to frame this amendment request solely in terms of inventorship, they in fact ask the Court "to deem Teva's pleadings amended with a count for patent invalidity under 35 U.S.C. § 102(f)." ECF No. 245 at 1. Thus, the correct inquiry here is whether Janssen gave express or implied consent to trying the issue of invalidity based upon incorrect inventorship.

raising a section 102(f) invalidity challenge. As Janssen noted in its opening post-trial brief, "Teva has not asserted an inventorship defense pursuant to 35 U.S.C. § 102(f)" prior to its pending motion. Pls. Br. at 74. Thus, Janssen did not raise any arguments against a section 102(f) challenge in any of its post-trial submissions, as would be expected if the issue had been raised, or if evidence relevant to such a challenge had been presented at trial. *Id*.

In determining whether there was implied consent to try an issue, the court must consider "whether the parties recognized that the unpleaded issue entered the case at trial, whether the evidence that supports the unpleaded issue was introduced at trial without objection, and whether a finding of trial by consent prejudiced the opposing party's opportunity to respond." *Liberty Lincoln-Mercury, Inc. v. Ford Motor Co.*, 676 F.3d 318, 327 (3d Cir. 2012) (internal citations and quotation marks omitted). Neither party appeared to recognize that a section 102(f) invalidity challenge entered the trial as this topic was never meaningfully discussed, and the only evidence and testimony relevant to inventorship heard at trial was presented in connection with adding Drs. Gopal and Samtani to the '906 Patent, as discussed above. Furthermore, "[t]he main consideration in determining whether leave to amend under Rule 15(b) should be granted is prejudice to the opposing party." *Swiatek*, 542 F. App'x at 188. Janssen argues persuasively that it would be greatly prejudiced by allowing Teva to amend its pleadings as it would "have prepared for and proceeded at trial much differently," including by calling witnesses and presenting evidence as to Drs. Lewyn-Briscoe and Kusumakar. ECF No. 252 at 18–19 (citing *Swiatek*, 542 F. App'x at 188).

While there are certainly fairness and prejudice concerns implicated by allowing Teva to assert a new invalidity defense approximately four months after closing arguments, six months after the close of briefing, and nine months after the conclusion of live testimony, the Court finds that even considering Teva's invalidity defense based upon incorrect inventorship, Teva has

clearly failed to carry its burden on this point. The trial record contains testimony and evidence which support granting Janssen's motion to correct inventorship by adding Drs. Samtani and Gopal as inventors (as discussed and analyzed above), but the record is devoid of any testimony or evidence showing that there are additional issues with inventorship of the '906 Patent. Teva attempts to avoid this dearth of support by citing to arguments outside of the trial record, largely focused on Janssen's withdrawn initial motion to correct inventorship. Such attempt to rely on materials outside of the trial record is improper and is rejected. *See Mass Engineered Design, Inc. v. Planar Sys., Inc*., No. 16-1510, 2018 WL 3323762, at *5 (D. Or. July 6, 2018) ("Moreover, at the bench trial, the Court will only consider admissible evidence in making its findings of fact and conclusions of law."); *Deere & Co. v. FIMCO Inc.*, 260 F. Supp. 3d 830, 835 (W.D. Ky. 2017) ("Initially, the Court notes that both parties should be mindful that this case is set for a bench trial rather than a jury trial. As such, the Court can and will only consider the evidence it has found to be relevant and admissible at trial."); *Armco, Inc. v. Burns & McDonnell, Inc*., 809 F. Supp. 43, 45 n.3 (S.D. Ohio 1992) ("At the bench trial of this case, this Court will be careful to only consider evidence ultimately admitted into evidence in rendering its decision."); *see also Caldwell-Baker Co. v. S. Illinois Railcar Co.*, 225 F. Supp. 2d 1243, 1259 (D. Kan. 2002) ("Withdrawal of a motion has a practical effect as if the party had never brought the motion."). Here, the Court must determine whether Teva has shown by clear and convincing admissible evidence that the '906 Patent is invalid for failing to name the correct inventors. *See Pannu*, 155 F.3d at 1350 ("When a party asserts invalidity under § 102(f) due to nonjoinder, a district court should first determine whether there exists clear and convincing proof that the alleged unnamed inventor was in fact a co-inventor."). The Court finds that Teva has not done so.

Teva's section 102(f) invalidity challenge relies almost exclusively on testimony and

evidence presented during its cross-examination of Janssen's witnesses that briefly addressed named and unnamed individuals' work on developing Invega Sustenna. These cursory exchanges regarding "teamwork," and touching upon other individuals who worked in largely unspecified capacities on Invega Sustenna, are wholly inadequate to support a section 102(f) challenge. *See* Trial Tr. (Vermeulen) at 755:11–16, 1004:21–1005:5, 1005:18–21, 1013:14–17, and 1024:13–17; *see also* Trial Tr. (Gopal) at 1172:3–16. This testimony does not show that a correct inventor of the '906 Patent has been omitted as clearly not every person who works on an invention that is later patented is an inventor in the eyes of the law. *Fina Oil & Chem. Co.*, 123 F.3d at 1473 ("[T]o be a joint inventor, an individual must make a contribution to the conception of the claimed invention that is not insignificant in quality, when that contribution is measured against the dimension of the full invention."). Teva presents no persuasive argument or evidence to show that any of the other individuals involved with Invega Sustenna should be named as inventors, as mere testimony confirming that individuals worked on a project in some capacity falls woefully short of the required clear and convincing evidence required to show inventorship is incorrect. *See, e.g.*, *Gemstar-TV Guide Int'l, Inc. v. Int'l Trade Comm'n*, 383 F.3d 1352, 1382 (Fed. Cir. 2004) ("[A]lleged co-inventors must prove their contribution to the conception of the invention with more than their own testimony concerning the relevant facts.").

Additionally, while Teva states without any legal or factual support that inventorship of the '906 Patent is "uncorrectable," (ECF No. 245 at 4), the Court rejects this meritless argument. It is well-settled that even if the Court were to find incorrect inventorship, Janssen would be given an opportunity remedy this issue. *See Pannu*, 155 F.3d at 1350 ("Upon such a finding of incorrect inventorship, a patentee may invoke section 256 to save the patent from invalidity. Accordingly, the patentee must then be given an opportunity to correct inventorship pursuant to that section.");

Roche Palo Alto LLC v. Ranbaxy Lab'ys Ltd., 551 F. Supp. 2d 349, 359 (D.N.J. 2008) (A patent owner is "entitled to an opportunity to correct inventorship through the district court, even if it did absolutely nothing to correct the improper inventorship beforehand"). While Teva has failed to meet its burden on its section 102(f) challenge, it has also failed to show that Janssen would not be able to cure inventorship.

Accordingly, the Court has considered Teva's invalidity challenge under section 102(f) despite the issues noted with its motion to amend the pleadings pursuant to Rule 15(b)(2) (ECF No. 244), and finds that the trial record does not contain adequate evidence or testimony to show that the '906 Patent is invalid due to failure to include all proper inventors.

IV. CONCLUSION

For the foregoing reasons, the Court finds that Defendant has failed to show by clear and convincing evidence that the Patent-in-Suit is invalid. An appropriate Order accompanies this Opinion.

DATE: October 8, 2021

s/ Claire C. Cecchi
CLAIRE C. CECCHI, U.S.D.J.

UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

JANSSEN PHARMACEUTICALS, INC. and JANSSEN PHARMACEUTICA NV, Plaintiffs, v. TEVA PHARMACEUTICALS USA, INC., Defendant.	Civil Action No.: 18-734 **ORDER**

CECCHI, District Judge.

This patent case was brought by Plaintiffs Janssen Pharmaceuticals, Inc. and Janssen Pharmaceutica NV (collectively, "Plaintiffs" or "Janssen") against Defendant Teva Pharmaceuticals USA, Inc. ("Defendant" or "Teva"). It appearing that:

1. Defendant has asserted invalidity of Claims 1–21 of U.S. Patent No. 9,439,906 (the "'906 Patent").
2. Defendant does not contest infringement of Claims 1–21 in accordance with the June 8, 2020 Stipulation and Order based on Defendant's submission of Abbreviated New Drug Application No. 211149 which seeks United States Food and Drug Administration approval to market generic versions of Invega Sustenna. ECF No. 88 at 1–2.
3. The Court held a two-week bench trial in this matter that began on October 13, 2020 and concluded on October 30, 2020. ECF Nos. 135–37, 140–41, 145–49, 151. During the bench trial, both parties made motions for judgment on partial findings pursuant to Federal Rule of Civil Procedure 52(c) (ECF Nos. 138, 150) and both parties opposed these motions (ECF Nos. 142, 164, 167). The parties submitted post-trial briefing and

proposed findings of fact and conclusions of law in December 2020. ECF Nos. 164, 165, 167, 167-1 (corrected at 168-1). On January 8, 2021, the parties submitted responsive briefs. ECF Nos. 188, 189. Closing arguments were held on March 5, 2021. ECF No. 199.

4. On December 11, 2020, Plaintiffs filed a Motion to Correct Inventorship Pursuant to 35 U.S.C. §256(b) after the conclusion of the bench trial. ECF No. 166. The parties addressed this motion in their post-trial and responsive briefing. ECF Nos. 164, 167, 188, and 189.

5. On July 7, 2021, Defendant filed a Motion to Amend pursuant to Federal Rule of Civil Procedure 15(b)(2), to deem Teva's pleadings amended with a count for patent invalidity under 35 U.S.C. § 102(f). ECF No. 244. Plaintiffs filed a brief in opposition on August 2, 2021 (ECF No. 252) and Defendant filed a reply in support on August 9, 2021 (ECF No. 258).

Accordingly, for the reasons set forth in this Court's accompanying Opinion,

IT IS on this 8th day of October, 2021

ORDERED that no finding of invalidity shall issue as to the '906 Patent; and it is further

ORDERED that pursuant to the June 8, 2020 Stipulation and Order of Infringement, Defendant infringes Claims 1–21 of the '906 Patent; and it is further

ORDERED that the parties' motions for judgment on partial findings pursuant to Federal Rule of Civil Procedure 52(c) (ECF Nos. 138, 150) are **DENIED**; and it is further

ORDERED that Plaintiffs' Motion to Correct Inventorship Pursuant to 35 U.S.C. §256(b) (ECF No. 166) is **GRANTED**; and it is further

ORDERED that Defendant's Motion to Amend pursuant to Federal Rule of Civil Procedure 15(b)(2), to deem Teva's pleadings amended with a count for patent invalidity under 35 U.S.C. § 102(f) (ECF No. 244) is **DENIED**; and it is further

ORDERED that the parties are directed to submit a joint proposed form of judgment consistent with this Order and the accompanying Opinion within thirty (30) days of the date of this Order; and it is further

ORDERED that an unredacted version of this Court's Opinion shall be filed under temporary seal and the parties shall submit a joint submission indicating the portions of this Court's Opinion that they seek to have redacted, as well as a statement of reasons as to why each redaction is necessary, within seven (7) days of the date of this Order.

SO ORDERED.

s/ Claire C. Cecchi

CLAIRE C. CECCHI, U.S.D.J.

(12) **United States Patent**
Vermeulen et al.

(10) **Patent No.: US 9,439,906 B2**
(45) **Date of Patent: Sep. 13, 2016**

(54) **DOSING REGIMEN ASSOCIATED WITH LONG ACTING INJECTABLE PALIPERIDONE ESTERS**

(75) Inventors: **An Vermeulen**, Beerse (BE); **Alfons Wouters**, Beerse (BE)

(73) Assignee: **Janssen Pharmaceutica NV** (BE)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 770 days.

(21) Appl. No.: **12/337,144**

(22) Filed: **Dec. 17, 2008**

(65) **Prior Publication Data**

US 2009/0163519 A1 Jun. 25, 2009

Related U.S. Application Data

(60) Provisional application No. 61/014,918, filed on Dec. 19, 2007, provisional application No. 61/120,276, filed on Dec. 5, 2008.

(51) **Int. Cl.**

C07D 471/04	(2006.01)
A61K 31/445	(2006.01)
A61K 31/41	(2006.01)
A61K 31/42	(2006.01)
A61K 31/519	(2006.01)

(52) **U.S. Cl.**

CPC ***A61K 31/519*** (2013.01)

(58) **Field of Classification Search**

CPC . A61K 31/519; A61K 9/0019; A61K 9/0024
USPC 514/257, 323, 360, 379
See application file for complete search history.

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Primary Examiner Sreeni Padmanabhan
Assistant Examiner — Jody Karol

(57) **ABSTRACT**

The present invention provides a method of treating patients in need of treatment with long acting injectable paliperidone palmitate formulations.

21 Claims, 3 Drawing Sheets

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FIG. 1

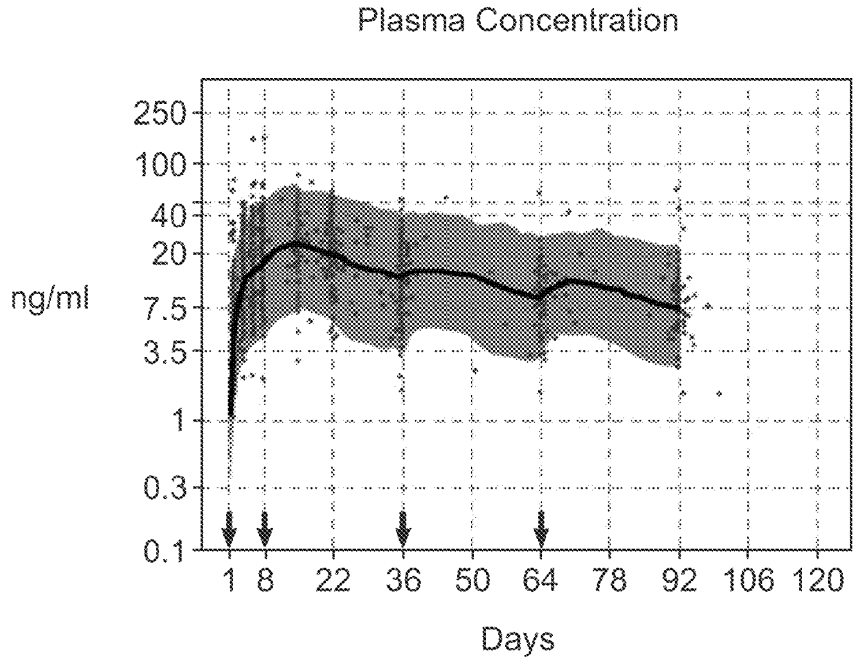

Plasma Concentration
ng/ml
250
100
40
20
7.5
3.5
1
0.3
0.1
1 8 22 36 50 64 78 92 106 120
Days

FIG. 2

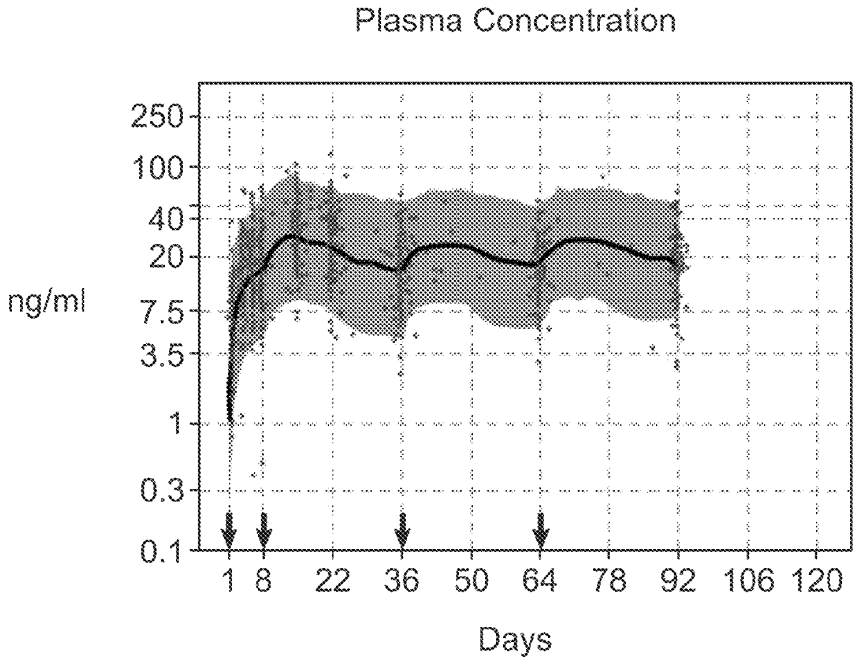
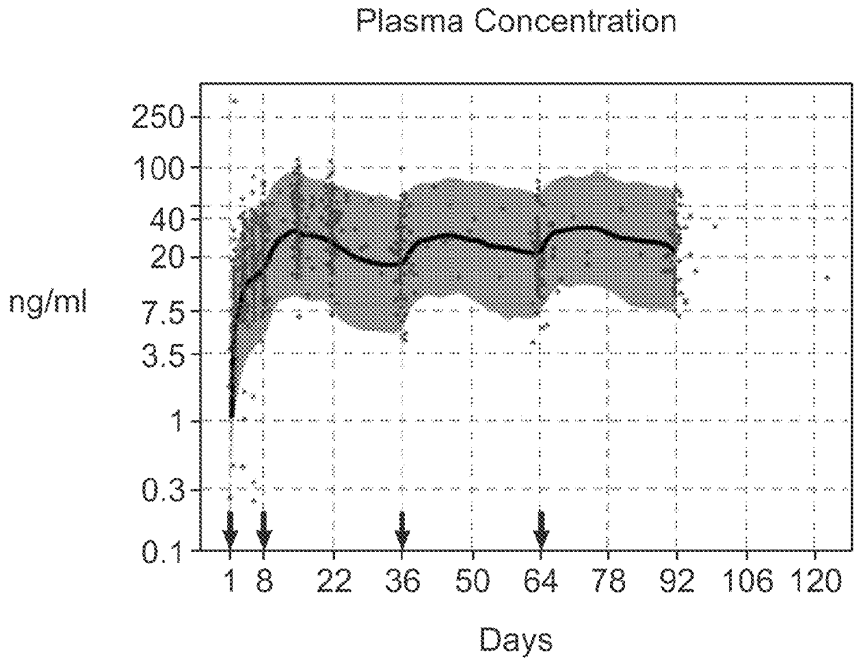

Plasma Concentration
ng/ml
250
100
40
20
7.5
3.5
1
0.3
0.1
1 8 22 36 50 64 78 92 106 120
Days

FIG. 3


Plasma Concentration
ng/ml
250
100
40
20
7.5
3.5
1
0.3
0.1
1 8 22 36 50 64 78 92 106 120
Days

DOSING REGIMEN ASSOCIATED WITH LONG ACTING INJECTABLE PALIPERIDONE ESTERS

CROSS REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of U.S. Provisional Application 61/014,918, filed on Dec. 19, 2007 and U.S. Provisional Application 61/120,276, filed on Dec. 5, 2008.

FIELD OF THE INVENTION

This invention relates to a method of treating patients in need of treatment with long acting injectable paliperidone palmitate formulations.

BACKGROUND OF THE INVENTION

Antipsychotic medications are the mainstay in the treatment of schizophrenia, schizoaffective disorder, and schizophreniform disorders. Conventional antipsychotics were introduced in the mid-1950s. These typical or first generation drugs are usually effective in controlling the positive symptoms of schizophrenia, but are less effective in moderating the negative symptoms or the cognitive impairment associated with the disease. Atypical antipsychotics or second generation drugs, typified by risperidone and olanzapine, were developed in the 1990s, and are generally characterized by effectiveness against both the positive and negative symptoms associated with schizophrenia.

Paliperidone palmitate is the palmitate ester of paliperidone (9-hydroxy-risperidone), a monoaminergic antagonist that exhibits the characteristic dopamine D_2 and serotonin (5-hydroxytryptamine type 2A) antagonism of the second-generation, atypical antipsychotic drugs. Paliperidone is the major active metabolite of risperidone. Extended release (ER) osmotic controlled release oral delivery (OROS) paliperidone, as a tablet formulation, is marketed in the United States (U.S.) for the treatment of schizophrenia and maintenance of effect.

Paliperidone palmitate is being developed as a long-acting, intramuscular (i.m.), injectable aqueous nanosuspension for the treatment of schizophrenia and other diseases that are normally treated with antipsychotic mediations. Because of extreme low water solubility, paliperidone esters such as paliperidone palmitate dissolve slowly after an i.m. injection before being hydrolyzed to paliperidone and made available in the systemic circulation.

Many patients with these mental illnesses achieve symptom stability with available oral antipsychotic medications; however, it is estimated that up to 75% have difficulty adhering to a daily oral treatment regimen, i.e. compliance problems. Problems with adherence often result in worsening of symptoms, suboptimal treatment response, frequent relapses and re-hospitalizations, and an inability to benefit from rehabilitative and psychosocial therapies.

Paliperidone palmitate injection has been developed to provide sustained plasma concentrations of paliperidone when administered once monthly, which may greatly enhance compliance with dosing. Paliperidone palmitate was formulated as an aqueous nano suspension as is described in U.S. Pat. Nos. 6,577,545 and 6,555,544. However, after the data was analyzed from the clinical trials of this formulation it was discovered that the absorption of paliperidone from these injections was far more complex than was originally anticipated. Additionally, attaining a potential therapeutic plasma level of paliperidone in patients was discovered to be dependent on the site of injection until steady state concentration is reached. Due to the challenging nature of ensuring an optimum plasma concentration-time profile for treating patients with paliperidone it is desirable to develop a dosing regimen that fulfills this goal in patients in need of treatment.

SUMMARY OF THE INVENTION

In one embodiment of the present invention there is provided a dosing regimen for administering paliperidone esters to a psychiatric patient in need of treatment comprising administering intramuscularly in the deltoid a first loading dose from about 100 mg-eq. to about 150 mg-eq. of paliperidone as a paliperidone palmitate formulated in a sustained release formulation on the first day of treatment; administering intramuscularly a second loading dose from about 100 mg to about 150 mg-eq of paliperidone as a paliperidone palmitate formulated in a sustained release formulation between about the 6th to 10th day of treatment; and administering intramuscularly in the gluteal a maintenance dose of about 25 to about 150 mg-eq. of paliperidone as a paliperidone ester in a sustained release formulation on between about the 34^{th} and about the 38th day of treatment.

In one embodiment of the present invention there is provided a dosing regimen for administering paliperidone esters to a psychiatric patient in need of treatment comprising administering intramuscularly in the deltoid a first loading dose from about 100 mg-eq. to about 150 mg-eq. of paliperidone as a paliperidone palmitate formulated in a sustained release formulation on the first day of treatment; administering intramuscularly a second loading dose from about 100 mg to about 150 mg-eq of paliperidone as a paliperidone palmitate formulated in a sustained release formulation between about the 6th to 10th day of treatment; and administering intramuscularly in the gluteal a maintenance dose of about 25 to about 150 mg-eq. of paliperidone as a paliperidone ester in a sustained release formulation approximately monthly from the date of the second loading dose.

In another embodiment of the present invention there is provided a dosing regimen for administering paliperidone palmitate to a psychiatric patient in need of treatment comprising administering intramuscularly in the deltoid of a patient in need of treatment a first loading dose from about 100 mg-eq. to about 150 mg-eq of paliperidone as paliperidone palmitate formulated in a sustained release formulation on the first day of treatment; administering intramuscularly in the deltoid muscle of the patient in need of treatment a second loading dose from about 100 mg-eq. to about 150 mg-eq. of paliperidone as paliperidone palmitate formulated in a sustained release formulation on the eighth day of treatment; and administering intramuscularly in the deltoid or gluteal muscle of the patient in need of treatment a maintenance dose of about 25 mg-eq. to about 75 mg-eq. of paliperidone as paliperidone palmitate in a sustained release formulation on between about the 34th day and the 38th day of treatment.

In another embodiment of the present invention there is provided a dosing regimen for administering paliperidone palmitate to a psychiatric patient in need of treatment comprising administering intramuscularly in the deltoid of a patient in need of treatment a first loading dose of about 150 mg-eq of paliperidone as paliperidone palmitate formulated in a sustained release formulation on the first day of treatment; administering intramuscularly in the deltoid muscle of

the patient in need of treatment a second loading dose from about 100 mg-eq. of paliperidone as paliperidone palmitate formulated in a sustained release formulation on the eighth day of treatment; and administering intramuscularly in the deltoid or gluteal muscle of the patient in need of treatment a maintenance dose of about 25 mg-eq. to about 75 mg-eq. of paliperidone as paliperidone palmitate in a sustained release formulation approximately monthly from the date of the second loading dose.

In another embodiment of the present invention there is provided a dosing regimen for administering paliperidone palmitate to a psychiatric patient in need of treatment comprising administering intramuscularly in the deltoid of a patient in need of treatment a first loading dose of about 150 mg-eq of paliperidone as paliperidone palmitate formulated in a sustained release formulation on the first day of treatment; administering intramuscularly in the deltoid muscle of the patient in need of treatment a second loading dose from about 100 mg-eq. of paliperidone as paliperidone palmitate formulated in a sustained release formulation on the eighth day of treatment; and administering intramuscularly in the deltoid or gluteal muscle of the patient in need of treatment a maintenance dose of about 75 mg-eq. of paliperidone as paliperidone palmitate in a sustained release formulation approximately monthly from the date of the second loading dose.

In yet another embodiment of the present invention there is provided a dosing regimen for administering paliperidone esters to a renally impaired psychiatric patient in need of treatment comprising administering intramuscularly in the deltoid a first loading dose of about 75 mg-eq of paliperidone as a paliperidone palmitate formulated in a sustained release formulation on the first day of treatment; administering intramuscularly a second loading dose of about 75 mg-eq of paliperidone as a paliperidone palmitate formulated in a sustained release formulation between about the 6th to 10th day of treatment; and administering intramuscularly in the gluteal a maintenance dose of about 25 mg-eq. to about 75 mg-eq of paliperidone as a paliperidone palmitate in a sustained release formulation on between about the 34^{th} and about the 38th day of treatment.

In yet another embodiment of the present invention there is provided a dosing regimen for administering paliperidone esters to a renally impaired psychiatric patient in need of treatment comprising administering intramuscularly in the deltoid a first loading dose of about 100 mg-eq of paliperidone as a paliperidone palmitate formulated in a sustained release formulation on the first day of treatment; administering intramuscularly a second loading dose of about 75 mg-eq of paliperidone as a paliperidone palmitate formulated in a sustained release formulation between about the 6th to 10th day of treatment; and administering intramuscularly in the gluteal a maintenance dose of about 25 mg-eq. to about 75 mg-eq of paliperidone as paliperidone palmitate in a sustained release formulation approximately monthly from the date of the second loading dose.

In a further embodiment of the present invention there is provided a dosing regimen for administering paliperidone palmitate to a psychiatric patient in need of treatment comprising administering intramuscularly in the deltoid of a patient in need of treatment a first loading dose of about 75 mg-eq. of paliperidone as paliperidone palmitate formulated in a sustained release formulation on the first day of treatment; administering intramuscularly in the deltoid muscle of the patient in need of treatment a second loading dose of about 75 mg-eq of paliperidone as paliperidone palmitate formulated in a sustained release formulation on the eighth day of treatment; and administering intramuscularly in the deltoid or gluteal muscle of the patient in need of treatment a maintenance dose of from about 25 mg-eq. to about 50 mg-eq. of paliperidone as paliperidone palmitate in a sustained release formulation on about the 34th day and the 38th day of treatment.

In one embodiment of the present invention there is provided a dosing regimen for administering paliperidone esters to a psychiatric patient in need of treatment comprising administering intramuscularly in the deltoid a first loading dose of about 150 mg-eq. of paliperidone as a paliperidone palmitate formulated in a sustained release formulation on the first day of treatment; thereafter administering intramuscularly a second maintenance dose of from about 25 mg-eq. to about 100 mg-eq of paliperidone as a paliperidone palmitate formulated in a sustained release formulation between about the 6th to 10th day of treatment; and administering intramuscularly in the gluteal a maintenance dose of about 25 to about 100 mg-eq. of paliperidone as a paliperidone palmitate in a sustained release formulation on between about the 34^{th} and about the 38th day of treatment.

In a further embodiment of the present invention there is provided a dosing regimen for administering paliperidone palmitate to a psychiatric patient in need of treatment comprising administering intramuscularly in the deltoid of a patient in need of treatment a first loading dose from about 150 mg-eq. of paliperidone as a paliperidone palmitate ester in a sustained release formulation on the first day of treatment; thereafter administering intramuscularly in the deltoid muscle of the patient in need of treatment a maintenance dose from about 25 mg-eq. to about 100 mg-eq. of paliperidone as paliperidone palmitate formulated in a sustained release formulation on the eighth day of treatment; and administering intramuscularly in the deltoid or gluteal muscle of the patient in need of treatment a maintenance dose of about 25 mg-eq. to about 100 mg-eq. of paliperidone as paliperidone palmitate in a sustained release formulation on about the 34th day and the 38th day of treatment.

This and other objects and advantages of the present invention may be appreciated from a review of the present applications.

BRIEF DESCRIPTION OF THE FIGURES

FIG. **1** shows the observed versus the population pharmacokinetics model simulation for plasma paliperidone concentrations for paliperidone palmitate 150 mg eq. in the deltoid on day 1, followed by 25 mg eq. in either the deltoid or gluteus on days 8, 36, and 64.

FIG. **2** shows the observed versus the population pharmacokinetics model simulation for plasma paliperidone concentrations for paliperidone palmitate 150 mg eq. in the deltoid on day 1, followed by 100 mg eq. in either the deltoid or gluteus on days 8, 36, and 64.

FIG. **3** shows the observed versus the population pharmacokinetics model simulation for plasma paliperidone concentrations for paliperidone palmitate 150 mg eq. in the deltoid on day 1, followed by 150 mg eq. in either the deltoid or gluteus on days 8, 36, and 64.

DETAILED DESCRIPTION

We have discovered after extensive analysis of the clinical data that paliperidone palmitate due to its dissolution rate-limited absorption exhibits flip-flop kinetics, where the apparent half-life is controlled by the absorption rate con-

stant. Additionally the volume of injected drug product also impacts the apparent rate constant. It was also discovered that deltoid injections result in a faster rise in initial plasma concentration, facilitating a rapid attainment of potential therapeutic concentrations. Consequently, to facilitate patients' attaining a rapid therapeutic concentration of paliperidone it is preferred to provide the initial loading dose of paliperidone palmitate in the deltoids. The loading dose should be from about 100 mg-eq. to about 150 mg-eq. of paliperidone provided in the form of paliperidone palmitate. After the first or more preferably after the second loading dose injection patients will be approaching a steady state concentration of paliperidone in their plasma and may be injected in either the deltoid or the gluteal muscle thereafter. However, it is preferred that the patients receive further injections in the gluteal muscle.

In view of these discoveries the recommended dosing regimen for patients to attain a therapeutic plasma level of paliperidone is for patients to receive the first dose of paliperidone palmitate on day 1 of treatment, followed by a second dose between days 6 to 10 of treatment, then a third dose between days 34 to 38 of treatment or monthly ±7 days after the second dose. More preferably the patients will be administered a first dose on day 1, a second dose on day 8 and a third dose on or about day 36 of treatment or approximately monthly ±3 days after the second dose. The first two doses will preferably be injected in the deltoid muscle. Thereafter paliperidone palmitate will be administered by injection approximately once a month (e.g. monthly ±7 days or approximately once every four weeks) thereafter. To assure that a potential therapeutic plasma level of paliperidone is attained at least a first loading dose of 150 mg-eq of paliperidone as a paliperidone palmitate ester should be administered on day one of treatment. Preferably the first two doses will be loading dose of between from about 100 mg-eq. to about 150 mg-eq. of paliperidone as a paliperidone palmitate ester to assure that a potential therapeutic plasma level of paliperidone is attained by the patient. The subsequent doses thereafter will drop to a therapeutic maintenance dose of from about 25 mg-eq. to 150 mg-eq. per month (±7 days). Preferably the maintenance dose will be from about 25 mg eq. to about 100 mg eq; more preferably the maintenance dose will be from about 25 mg eq. to about 75 mg eq; and most preferably the maintenance dose initially will be about 50 mg eq., or more preferably the maintenance dose initially will be about 75 mg eq. which may be administered intramuscularly into the deltoid or gluteal muscle, but more preferably will be administered in the gluteal muscle. Those of ordinary skill in the art will understand that the maintenance dose may be titrated up or down in view of the patients condition (response to the medication and renal function).

Since paliperidone is mainly eliminated through the kidneys, patients with renal impairment will have a higher total exposure to paliperidone after i.m. injections of paliperidone palmitate. For patients with renal impairment it would desirable to adjust the loading doses to account for the increased exposure levels of patients with renal impairment. For patients with mild renal impairment the loading doses should be reduced to 75 mg-eq. for the first two loading doses. The maintenance doses should range from about 25 mg-eq. to about 75 mg-eq. and more preferably with range from about 25 mg-eq. to about 50 mg-eq. The doses would be administered on day 1 of treatment, followed by a second dose between days 6 to 10 of treatment, then a third dose between days 34 to 38 of treatment. More preferably the patients will be administered a first dose on day 1, a second dose on day 8 and a third dose on day 36 of treatment. The first two doses will preferably be injected in the deltoid muscle. Thereafter paliperidone palmitate will be administered by injection approximately once a month (e.g. one a month ±7 days or once every four weeks) thereafter. For the purpose of this patent application renal function is estimated by glomerular filtration rate (GFR) usually measured by the creatinine clearance (best calculated from a 24-hour urine collection). Creatine clearance may be estimated by the Cockcroft and Gault method based on serum creatinine concentration, as described in Prediction of creatinine clearance from serum creatinine. Nephron 1976; vol 16. pages 31-41. Patients with mild renal impairment have a creatinine clearance of 50 to <80 mL/minute.

It is recommended that the second initiation dose of paliperidone palmitate be given about one week (6-10 days) after the first dose. To avoid a missed dose, patients may be given the second dose 2 days before or after the one-week time point. Similarly, the third and subsequent injections after the initiation regimen are recommended to be given monthly. To avoid a missed monthly dose, patients may be given the injection up to 7 days before or after the monthly time point.

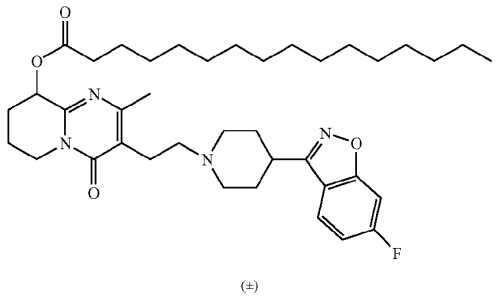
After initiation, the recommended injection cycle of paliperidone palmitate is monthly. If less than 6 weeks have elapsed since the last injection, then the previously stabilized dose should be administered as soon as possible, followed by injections at monthly intervals.

If more than 6 weeks have elapsed since the last injection, reinitiation with the same dose the patient was previously stabilized to should be resumed in the following manner: 1) a deltoid injection as soon as practically possible, followed by 2) another deltoid injection one week later, and 3) resumption of either deltoid or gluteal dosing at monthly intervals.

If more than 6 months have elapsed since the last injection, it is recommended to re-initiate dosing as described above.

Additionally, in this patient population needle length and BMI index are two related variables that need to be considered to assure patients attain therapeutic concentration of paliperidone in the desired time frame. Patients with high BMI had lower plasma concentration of paliperidone and a lessened treatment response. The lower initial plasma concentration in high BMI patients was likely due to unintended partial or complete injection into adipose tissue, instead of deep injection into muscle. However, once steady-state plasma concentration are attained BMI no longer influenced plasma concentrations or clinical efficacy. From these observations it was determined that for patients weighing <90 kg (<200 lb) a 1-inch needle will be of adequate length to use in injections to reach the muscle tissue for deltoid injections with preferably a 23 gauge needle. However, for patients with high BMIs, ≥90 kg (≥200 lb) a 1.5-inch needle should be used for deltoid injections. For gluteal muscle injections a 1.5-inch needle should be used. Preferably the 1.5-inch needle will be a 22-gauge needle.

Paliperidone esters are psychotic agents belonging to the chemical class of benzisoxazole derivatives, which contains a racemic mixture of (+)- and (−)-paliperidone, which are described in U.S. Pat. No. 5,254,556 (incorporated herein by reference). The chemical name for paliperidone palmitate is (±)-3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl] ethyl]-6,7,8,9-tetrahydro-2-methyl-4-oxo-4H-pyrido[1,2-α] pyrimidin-9-yl hexadecanoate. The structural formula is:



(±)

Paliperidone esters may be formulated with pharmaceutical excipients into injectable dosage forms as described in U.S. Pat. No. 5,254,556 and U.S. Pat. No. 6,077,843 (incorporated herein by reference). Injectable formulations may be formulated in aqueous carriers.

Currently it is preferred to administer paliperidone palmitate in a once monthly aqueous depot. Suitable aqueous depot formulations are described in U.S. Pat. No. 6,077,843 (incorporated herein by reference). The aqueous formulation would preferably be a nano particle suspension of wherein the nano particles would be of an averages size of less than 2000 nm to about 100 nm. Preferably the nano particles would have an average particle size (d50) of from about 1600 nm to 400 nm and most preferably about 1400 nm to 900 nm. Preferably the d90 will be less than about 5000 nm and more preferably less than about 4400 nm. As used herein, an effective average particle size (d50) of less than 2,000 nm means that at least 50% of the particles have a diameter of less than 2,000 nm when measured by art-known conventional techniques, such as sedimentation field flow fractionation, photon correlation spectroscopy or disk centrifugation. With reference to the effective average particle size, it is preferred that at least 90%, e.g. 5,000 nm. Most preferably, 90% of the particles have a size of less than 4,400 nm.

Suitable aqueous nano particle depot formulations are described in U.S. Pat. No. 6,555,544 (incorporated herein by reference). In one embodiment of the present invention the formulation would comprise nanoparticles, a surfactant, a suspending agent, and optionally one or more additional ingredients selected from the group consisting of preservatives, buffers and an isotonizing agents.

Useful surface modifiers are believed to include those that physically adhere to the surface of the active agent but do not chemically bond thereto.

Suitable surface modifiers can preferably be selected from known organic and inorganic pharmaceutical excipients. Such excipients include various polymers, low molecular weight oligomers, natural products and surfactants. Preferred surface modifiers include nonionic and anionic surfactants. Representative examples of excipients include gelatin, casein, lecithin (phosphatides), gum acacia, cholesterol, tragacanth, stearic acid, benzalkonium chloride, calcium stearate, glyceryl monostearate, cetostearyl alcohol, cetomacrogol emulsifying wax, sorbitan esters, polyoxyethylene alkyl ethers, e.g., macrogol ethers such as cetomacrogol 1000, polyoxyethylene castor oil derivatives, polyoxyethylene sorbitan fatty acid esters, e.g., the commercially available TWEENS™, polyethylene glycols, polyoxyethylene stearates, colloidal silicon dioxide, phosphates, sodium dodecylsulfate, carboxymethylcellulose calcium, carboxymethylcellulose sodium, methylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose phtalate, noncrystalline cellulose, magnesium aluminate silicate, triethanolamine, polyvinyl alcohol (PVA), poloxamers, tyloxapol and polyvinylpyrrolidone (PVP). Most of these excipients are described in detail in the Handbook of Pharmaceutical Excipients, published jointly by the American Pharmaceutical Association and The Pharmaceutical Society of Great Britain, the Pharmaceutical Press, 1986. The surface modifiers are commercially available and/or can be prepared by techniques known in the art. Two or more surface modifiers can be used in combination.

Particularly preferred surface modifiers include polyvinylpyrrolidone; tyloxapol; poloxamers, such as PLURONIC™. F68, F108 and F127 which are block copolymers of ethylene oxide and propylene oxide available from BASF; poloxamines, such as TETRONIC™ 908 (T908) which is a tetrafunctional block copolymer derived from sequential addition of ethylene oxide and propylene oxide to ethylenediamine available from BASF; dextran; lecithin; Aerosol OT™ (AOT) which is a dioctyl ester of sodium sulfosuccinic acid available from Cytec Industries; DUPONOL™ P which is a sodium lauryl sulfate available from DuPont; TRITON™ X-200 which is an alkyl aryl polyether sulfonate available from Rohm and Haas; TWEEN™. 20, 40, 60 and 80 which are polyoxyethylene sorbitan fatty acid esters available from ICI Specialty Chemicals; SPAN™ 20, 40, 60 and 80 which are sorbitan esters of fatty acids; ARLACEL™ 20, 40, 60 and 80 which are sorbitan esters of fatty acids available from Hercules, Inc.; CARBOWAX™ 3550 and 934 which are polyethylene glycols available from Union Carbide; CRODESTA™ F110 which is a mixture of sucrose stearate and sucrose distearate available from Croda Inc.; CRODESTA™ SL-40 which is available from Croda, Inc.; hexyldecyl trimethyl ammonium chloride (CTAC); bovine serum albumin and SA90HCO which is $C_{18}H_{17}CH_2(CON(CH_3)CH_2(CHOH)_4CH_2OH)_2$. The surface modifiers which have been found to be particularly useful include tyloxapol and a poloxamer, preferably, Pluronic™ F108 and Pluronic™ F68.

Pluronic™ F108 corresponds to poloxamer 338 and is the polyoxyethylene, polyoxypropylene block copolymer that conforms generally to the formula $HO[CH_2\ CH_2O]_x[CH(CH_3)CH_2O]_y[CH_2CH_2O]_z\ H$ in which the average values of x, y and z are respectively 128, 54 and 128. Other commercial names of poloxamer 338 are Hodag NONIONIC™ 1108-F available from Hodag, and SYNPERONIC™ PE/F108 available from ICI Americas.

The optimal relative amount of paliperidone palmitate and the surface modifier depends on various parameters. The optimal amount of the surface modifier can depend, for example, upon the particular surface modifier selected, the critical micelle concentration of the surface modifier if it forms micelles, the surface area of the antipsychotic agent, etc. The specific surface modifier preferably is present in an amount of 0.1 to 1 mg per square meter surface area of the paliperidone palmitate. It is preferred in the case of paliperidone palmitate (9-hydroxyrisperidone palmitate) to use PLURONIC™ F 108 as a surface modifier, a relative amount (w/w) of both ingredients of approximately 6:1 is preferred.

The particles of this invention can be prepared by a method comprising the steps of dispersing paliperidone palmitate in a liquid dispersion medium and applying mechanical means in the presence of grinding media to reduce the particle size of the antipsychotic agent to an effective average particle size of less than 2,000 nm. The

particles can be reduced in size in the presence of a surface modifier. Alternatively, the particles can be contacted with a surface modifier after attrition.

A general procedure for preparing the particles of this invention includes (a) obtaining paliperidone palmitate in micronized form; (b) adding the micronized paliperidone palmitate to a liquid medium to form a premix; and (c) subjecting the premix to mechanical means in the presence of a grinding medium to reduce the effective average particle size.

The paliperidone palmitate in micronized form may be prepared using techniques known in the art. It is preferred that the particle size of the micronized paliperidone palmitate be less than about 100 μm as determined by sieve analysis. If the particle size of the micronized paliperidone palmitate is greater than about 100 μm, then it is preferred that the particles of paliperidone palmitate be reduced in size to less than 100 μm.

The micronized paliperidone palmitate can then be added to a liquid medium in which it is essentially insoluble to form a premix. The concentration of paliperidone palmitate in the liquid medium (weight by weight percentage) can vary widely and depends on the selected antipsychotic agent, the selected surface modifier and other factors. Suitable concentrations of paliperidone palmitate in compositions vary between 0.1 to 60%, preferably is from 0.5 to 30%, and more preferably, is approximately 7% (w/v). It is currently preferred to use a concentration of about 100 mg eq of paliperidone per ml or about 156 mg of paliperidone palmitate per ml.

A more preferred procedure involves the addition of a surface modifier to the premix prior to its subjection to mechanical means to reduce the effective average particle size. The concentration of the surface modifier (weight by weight percentage) can vary from 0.1% to 90%, preferably from 0.5% to 80%, and more preferably is approximately 7% (w/v).

The premix can be used directly by subjecting it to mechanical means to reduce the effective average particle size in the dispersion to less than 2,000 nm. It is preferred that the premix be used directly when a ball mill is used for attrition. Alternatively, the antipsychotic agent and, optionally, the surface modifier, can be dispersed in the liquid medium using suitable agitation such as, for example, a roller mill or a Cowles type mixer, until a homogeneous dispersion is achieved.

The mechanical means applied to reduce the effective average particle size of the antipsychotic conveniently can take the form of a dispersion mill. Suitable dispersion mills include a ball mill, an attritor mill, a vibratory mill, a planetary mill, media mills—such as a sand mill and a bead mill. A media mill is preferred due to the relatively shorter milling time required to provide the desired reduction in particle size. For media milling, the apparent viscosity of the premix preferably is anywhere between 0.1 and 1 Pa·s. For ball milling, the apparent viscosity of the premix preferably is anywhere between 1 and 100 mPa·s.

The grinding media for the particle size reduction step can be selected from rigid media preferably spherical or particulate in form having an average size less than 3 mm and, more preferably, less than 1 mm. Such media desirably can provide the particles of the invention with shorter processing times and impart less wear to the milling equipment. The selection of the material for the grinding media is believed not to be critical. However, 95% ZrO stabilized with magnesia, zirconium silicate, and glass grinding media provide particles having levels of contamination which are acceptable for the preparation of pharmaceutical compositions. Further, other media, such as polymeric beads, stainless steel, titania, alumina and 95% ZrO stabilized with yttrium, are useful. Preferred grinding media have a density greater than 2.5 g/cm.sup.3 and include 95% ZrO stabilized with magnesia and polymeric beads.

The attrition time can vary widely and depends primarily upon the particular mechanical means and processing conditions selected. For rolling mills, processing times of up to two days or longer may be required.

The particles must be reduced in size at a temperature which does not significantly degrade the antipsychotic agent. Processing temperatures of less than 30° C. to 40° C. are ordinarily preferred. If desired, the processing equipment may be cooled with conventional cooling equipment. The method is conveniently carried out under conditions of ambient temperature and at processing pressures which are safe and effective for the milling process.

The surface modifier, if it was not present in the premix, must be added to the dispersion after attrition in an amount as described for the premix above. Thereafter, the dispersion can be mixed by, for example, shaking vigorously. Optionally, the dispersion can be subjected to a sonication step using, for example, a ultrasonic power supply.

Aqueous compositions according to the present invention conveniently further comprise a suspending agent and a buffer, and optionally one or more of a preservative and an isotonizing agent. Particular ingredients may function as two or more of these agents simultaneously, e.g. behave like a preservative and a buffer, or behave like a buffer and an isotonizing agent.

Suitable suspending agents for use in the aqueous suspensions according to the present invention are cellulose derivatives, e.g. methyl cellulose, sodium carboxymethyl cellulose and hydroxypropyl methyl cellulose, polyvinylpyrrolidone, alginates, chitosan, dextrans, gelatin, polyethylene glycols, polyoxyethylene- and polyoxy-propylene ethers. Preferably sodium carboxymethyl cellulose is used in a concentration of 0.5 to 2%, most preferably 1% (w/v). Suitable wetting agents for use in the aqueous suspensions according to the present invention are polyoxyethylene derivatives of sorbitan esters, e.g. polysorbate 20 and polysorbate 80, lecithin, polyoxyethylene- and polyoxypropylene ethers, sodium deoxycholate. Preferably polysorbate 20 is used in a concentration of 0.5 to 3%, more preferably 0.5 to 2%, most preferably 1.1% (w/v).

Suitable buffering agents are salt of weak acids and should be used in amount sufficient to render the dispersion neutral to very slightly basic (up to pH 8.5), preferably in the pH range of 7 to 7.5. Particularly preferred is the use of a mixture of disodium hydrogen phosphate (anhydrous) (typically about 0.9% (w/v)) and sodium dihydrogen phosphate monohydrate (typically about 0.6% (w/v)). This buffer also renders the dispersion isotonic and, in addition, less prone to flocculation of the ester suspended therein.

Preservatives are antimicrobials and anti-oxidants which can be selected from the group consisting of benzoic acid, benzyl alcohol, butylated hydroxyanisole, butylated hydroxytoluene, chlorbutol, a gallate, a hydroxybenzoate, EDTA, phenol, chlorocresol, metacresol, benzethonium chloride, myristyl-gamma-piccolinium chloride, phenylmercuric acetate and thimerosal. In particular, it is benzyl alcohol which can be used in a concentration up to 2% (w/v), preferably up to 1.5% (w/v).

Isotonizing agents are, for example, sodium chloride, dextrose, mannitol, sorbitol, lactose, sodium sulfate. The suspensions conveniently comprise from 0 to 10% (w/v)

isotonizing agent. Mannitol may be used in a concentration from 0 to 7% More preferably, however, from about 1 to about 3% (w/v), especially from about 1.5 to about 2% (w/v) of one or more electrolytes are used to render the suspension isotonic, apparently because ions help to prevent flocculation of the suspended ester. In particular, electrolytes of the buffer serve as isotonizing agent.

A particularly desirable feature for an injectable depot formulation relates to the ease with which it can be administered. In particular such an injection should be feasible using a needle as fine as possible in a span of time which is as short as possible. This can be accomplished with the aqueous suspensions of the present invention by keeping the viscosity below about 75 mPa·s, preferably below 60 mPa·s. Aqueous suspensions of such viscosity or lower can both easily be taken up in a syringe (e.g. from a vial), and injected through a fine needle (e.g a 21 G 1½ inch, 22 G 2 inch, 22 G 1¼ inch or 23 G 1 inch needle). The preferred needles for injection are 22 G 22 G 1½ inch regular wall and 23 G 1½ inch regular wall needles.

Ideally, aqueous suspensions according to the present invention will comprise as much prodrug as can be tolerated so as to keep the injected volume to a minimum, and as little of the other ingredients as possible. In particular, such a composition will comprise by weight based on the total volume of the composition: (a) from 3 to 20% (w/v) of the prodrug; (b) from 0.5 to 2% (w/v) of a wetting agent; (c) one or more buffering agents sufficient to render the composition neutral to very slightly basic (pH 8.5); (d) from 0.5 to 2% (w/v) of a suspending agent; (e) up to 2% (w/v) preservatives; and (f) water q.s. ad 100%. Preferably the aqueous suspension will be made under sterile conditions and no preservatives will be used. Appropriate methods to aseptically prepare paliperidone palmitate are described in WO 2006/114384 which is hereby incorporated by reference herein.

The preferred aqueous dosage form contains inactive ingredients that are polysorbate 20, polyethylene glycol 4000, citric acid monohydrate, disodium hydrogen phosphate anhydrous, sodium dihydrogen phosphate monohydrate, sodium hydroxide, and water for injection. The mg of compound delivered in such a dosage form to the patient may be from 25 to about 150 mg (e.g. 25 mg, 50 mg, 75 mg, 100 mg, 150 mg) injectable dosage form.

The term "psychiatric patient" as used herein, refers to a human, who has been the object of treatment, or experiment for a "mental disorder" and "mental illness" refer to those provided in the Diagnostic and Statistical Manual (DSM IV), American Psychological Association (APA). Those of ordinary skill in the art will appreciate that paliperidone esters (e.g. paliperidone palmitate), can be administered to psychiatric patients for all the known uses of risperidone. These mental disorders include, but are not limited to, schizophrenia; bipolar disorder or other disease states in which psychosis, aggressive behavior, anxiety or depression is evidenced. Schizophrenia refers to conditions characterized as schizophrenia, schizoaffective disorder and schizophreniform disorders. in DSM-IV-TR such as category 295.xx. Bipolar Disorder refers to a condition characterized as a Bipolar Disorder, in DSM-IV-TR such as category 296.xx including Bipolar I and Bipolar Disorder II. The DSM-IV-TR was prepared by the Task Force on Nomenclature and Statistics of the American Psychiatric Association, and provides clear descriptions of diagnostic categories. Pathologic psychological conditions, which are psychoses or may be associated with psychotic features include, but are not limited to the following disorders that have been characterized in the DSM-IV-TR. Diagnostic and Statistical Manual of Mental Disorders, Revised, 3rd Ed. (1994). The numbers in parenthesis refer to the DSM-IV-TR categories. The skilled artisan will recognize that there are alternative nomenclatures, nosologies, and classification systems for pathologic psychological conditions and that these systems evolve with medical scientific progress. Examples of pathologic psychological conditions which may be treated include, but are not limited to, Mild Mental Retardation (317), Moderate Mental Retardation (318.0), Severe Mental Retardation (318.1), Profound Mental Retardation (318.2), Mental Retardation Severity Unspecified (319), Autistic Disorders (299.00), Rett's Disorder (299.80), Childhood Disintegrative Disorders (299.10), Asperger's Disorder (299.80), Pervasive Developmental Disorder Not Otherwise Specified (299.80), Attention-Deficit/Hyperactivity Disorder Combined Type (314.01), Attention-Deficit/Hyperactivity Disorder Predominately Inattentive Type (314.00), Attention-Deficit/Hyperactivity Disorder Predominately Hyperactive-Impulsive Type (314.01), Attention-Deficit/Hyperactivity Disorder NOS (314.9), Conduct Disorder (Childhood-Onset and Adolescent Type 312.8), Oppositional Defiant Disorder (313.81), Disruptive Behavior Disorder Not Otherwise Specified (312.9), Solitary Aggressive Type (312.00), Conduct Disorder, Undifferentiated Type (312.90), Tourette's Disorder (307.23), Chronic Motor Or Vocal Tic Disorder (307.22), Transient Tic Disorder (307.21), Tic Disorder NOS (307.20), Alcohol Intoxication Delirium (291.0), Alcohol Withdrawal Delirium (291.0), Alcohol-Induced Persisting Dementia (291.2), Alcohol-Induced Psychotic Disorder with Delusions (291.5), Alcohol-Induced Psychotic Disorder with Hallucinations (291.3), Amphetamine or Similarly Acting Sympathomimetic Intoxication (292.89), Amphetamine or Similarly Acting Sympathomimetic Delirium (292.81), Amphetamine or Similarly Acting Sympathomimetic Induced Psychotic with Delusions (292.11), Amphetamine or Similarly Acting Sympathomimetic Induced Psychotic with Hallucinations (292.12), Cannabis-Induced Psychotic Disorder with Delusions (292.11), Cannabis-Induced Psychotic Disorder with Hallucinations (292.12), Cocaine Intoxication (292.89), Cocaine Intoxication Delirium (292.81), Cocaine-Induced Psychotic Disorder with Delusions (292.11), Cocaine-Induced Psychotic Disorder with Hallucinations (292.12), Hallucinogen Intoxication (292.89), Hallucinogen Intoxication Delirium (292.81), Hallucinogen-Induced Psychotic disorder with Delusions (292.11), Hallucinogen-Induced Psychotic disorder with Delusions (292.12), Hallucinogen-Induced Mood Disorder (292.84), Hallucinogen-Induced Anxiety Disorder (292.89), Hallucinogen-Related Disorder Not Otherwise Specified (292.9), Inhalant Intoxication (292.89), Inhalant Intoxication Delirium (292.81), Inhalant-Induced Persisting Dementia (292.82), Inhalant-Induced Psychotic Disorder with Delusions (292.11), Inhalant-Induced Psychotic with Hallucinations (292.12), Inhalant-Induced Mood Disorder (292.89), Inhalant-Induced Anxiety Disorder (292.89), Inhalant-Related Disorder Not Otherwise Specified (292.9), Opioid Intoxication Delirium (292.81), Opioid-Induced Psychotic Disorder with Delusions (292.11), Opioid Intoxication Delirium (292.81), Opioid-Induced Psychotic Disorder with Hallucinations (292.12), Opioid-Induced Mood Disorder (292.84), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Intoxication (292.89), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Intoxication Delirium (292.81), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Induced Psychotic Disorder with Delusions (292.11), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Induced Psychotic Disorder with Hallucinations (292.12), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Mood Disorder (292.84), Phencyclidine (PCP) or

Similarly Acting Arylcyclohexylamine Induced Anxiety Disorder (292.89), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Related Disorder Not Otherwise Specified (292.9), Sedative, Hypnotic or Anxiolytic Intoxication (292.89), Sedation, Hypnotic or Anxiolytic Intoxication Delirium (292.81), Sedation, Hypnotic or Anxiolytic Withdrawal Delirium (292.81), Sedation, Hypnotic or Anxiolytic Induced Persisting Dementia (292.82), Sedation, Hypnotic or Anxiolytic-Induced Psychotic Disorder with Delusions (292.11), Sedation, Hypnotic or Anxiolytic-Induced Psychotic Disorder with Hallucinations (292.12), Sedation, Hypnotic or Anxiolytic-Induced Mood Disorder (292.84), Sedation, Hypnotic or Anxiolytic-Induced Anxiety Disorder (292.89), Other (or Unknown) Substance Intoxication (292.89), Other (or Unknown) Substance-Induced Delirium (292.81), Other (or Unknown) Substance-Induced Persisting Dementia (292.82), Other (or Unknown) Substance-Induced Psychotic Disorder with Delusions (292.11), Other (or Unknown) Substance-Induced Psychotic Disorder with Hallucinations (292.12), Other (or Unknown) Substance-Induced Mood Disorder (292.84), Other (or Unknown) Substance-Induced Anxiety Disorder (292.89), Other (or Unknown) Substance Disorder Not Otherwise Specified (292.9), Obsessive Compulsive Disorder (300.3), Post-traumatic Stress Disorder (309.81), Generalized Anxiety Disorder (300.02), Anxiety Disorder Not Otherwise Specified (300.00), Body Dysmorphic Disorder (300.7), Hypochondriasis (or Hypochondriacal Neurosis) (300.7), Somatization Disorder (300.81), Undifferentiated Somatoform Disorder (300.81), Somatoform Disorder Not Otherwise Specified (300.81), Intermittent Explosive Disorder (312.34), Kleptomania (312.32), Pathological Gambling (312.31), Pyromania (312.33), Trichotillomania (312.39), and Impulse Control Disorder NOS (312.30), Schizophrenia, Paranoid Type, (295.30), Schizophrenia, Disorganized (295.10), Schizophrenia, Catatonic Type, (295.20), Schizophrenia, Undifferentiated Type (295.90), Schizophrenia, Residual Type (295.60), Schizophreniform Disorder (295.40), Schizoaffective Disorder (295.70), Delusional Disorder (297.1), Brief Psychotic Disorder (298.8), Shared Psychotic Disorder (297.3), Psychotic Disorder Due to a General Medical Condition with Delusions (293.81), Psychotic Disorder Due to a General Medical Condition with Hallucinations (293.82), Psychotic Disorders Not Otherwise Specified (298.9), Major Depression, Single Episode, Severe, without Psychotic Features (296.23), Major Depression, Recurrent, Severe, without Psychotic Features (296.33), Bipolar Disorder, Mixed, Severe, without Psychotic Features (296.63), Bipolar Disorder, Mixed, Severe, with Psychotic Features (296.64), Bipolar Disorder, Manic, Severe, without Psychotic Features (296.43), Bipolar Disorder, Manic, Severe, with Psychotic Features (296.44), Bipolar Disorder, Depressed, Severe, without Psychotic Features (296.53), Bipolar Disorder, Depressed, Severe, with Psychotic Features (296.54), Bipolar II Disorder (296.89), Bipolar Disorder Not Otherwise Specified (296.80), Personality Disorders, Paranoid (301.0), Personality Disorders, Schizoid (301.20), Personality Disorders, Schizotypal (301.22), Personality Disorders, Antisocial (301.7), and Personality Disorders, Borderline (301.83).

The following non-limiting examples are provided to further illustrate the present invention.

The term "therapeutically effective amount" as used herein, means that amount of active compound or pharmaceutical agent that elicits the biological or medicinal response in human that is being sought by a researcher, medical doctor or other clinician, which includes alleviation of the symptoms of the disease or disorder being treated.

Those of skill in the treatment of diseases could easily determine the effective amount of paliperidone to administer for the treatment of the diseases listed above. In general it is contemplated that an effective amount of paliperidone for the treatment of mental disorders would be from about 0.01 mg/kg to about 2 mg/kg body weight. For the present invention it is preferred to dose patients with 25 mg-eq. to about 150 mg eq. paliperidone. The amount of paliperidone palmitate is provided in sufficient amount to provide the equivalent dose of paliperidone after the palmitic acid moiety is removed from the ester (e.g. 156 mg corresponds to paliperidone 100 mg). In one embodiment of present invention wherein paliperidone palmitate is administered by intramuscular injection once per month is preferred.

EXAMPLE 1

Paliperidone Palmitate Formulations

a) Crystallization in Stainless Steel Reactor of 50 L

All equipment was sterilized using dry heat sterilization.

A stainless steel reactor was charged with 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-9-hydroxy-2-methyl-4H-pyrido[1,2-a]-pyrimidin-4-one palmitate ester and ethanol parenteral grade (8 L/kg) and heated to reflux temperature (78-79° C.) while stirring. The product dissolved at about 70° C. The solution was filtered at 76° C. over a sterile 0.22 μm filter into a sterile crystallization reactor. The sterile filter was then washed with heated ethanol (1 L/kg).

The filtrate was reheated to reflux and then cooled to room temperature whereupon the product crystallized. The thus obtained suspension was reheated again. The solution was cooled using differing cooling gradients (in consecutive experiments, the mixture was reheated and cooled again; after each cooling gradient, a sample was taken and isolated using a filter. The crystals were dried in vacuo at 50° C. in Tyvek bags so as to prevent dust formation and the particle characteristics were determined.

Different batches were run, yielding product with a particle size distribution measured by laser diffraction as shown in Table 1.

TABLE 1

	Crystallization							
	Calculated cooling		start at . . .		start cooling	Particle size distribution		
Cooling rate	gradient (° C./min)	Tmax Treactor	(° C.) Treactor	Tjacket	(° C.) Treactor	d10 (μm)	d50 (μm)	d90 (μm)
1° C./min	0.95	78	63.5	60.2	77.5	156	65	16
ASAP	3.2	75.7	61.2	17.5	75	119	36	9.2
0.5° C./min	0.48	75.7	63.8	62.7	75	192	80	20

TABLE 1-continued

	Crystallization							
	Calculated cooling		start at . . .		start cooling	Particle size distribution		
Cooling rate	gradient (° C./min)	Tmax Treactor	(° C.) Treactor	Tjacket	(° C.) Treactor	dl10 (μm)	dl50 (μm)	dl90 (μm)
0.5° C./min	0.48	75.7	63.8	62.7	75	189	81	23
0.7° C./min	0.81	75.7	61.7	58.9	75	113	41	11
1° C./min	0.92	75.7	62.1	54.9	75	128	52	13

b) Formulation of Composition

Table 2 provides the formulation for the F013 formulation. The F011 formulation contained the same ingredients, with the exception of citric acid and NaOH, which were not present in the F011 formulation. Since the F011 formulation does not contain NaOH or citric acid, they are not part of the aqueous phase that is added to the milled concentrate of the F011 formulation. Therefore, the concentration of buffer salts in the aqueous phase of the F011 formulation is slightly different to make the formulation isotonic.

TABLE 2

	Amount Required	
Name	Per ml	Quantity for 24 L
Paliperidone palmitate (sterile grade)	156 mg	3.744 kg
Polysorbate 20 parenteral	12 mg	288 g
Citric acid monohydrate parenteral	5 mg	120 g
Disodium hydrogen phosphate anhydrous parenteral	5 mg	120 g
Sodium dihydrogen phosphate monohydrate parenteral	2.5 mg	60 g
Sodium Hydroxide all use	2.84 mg	68 g
Polyethylene Glycol 4000 parenteral	30 mg	720 g
Water for injections q.s. ad	1000 μl	24 L

Equipment

stainless steel (SS) containers

Grinding media (Zirconium beads)+stainless steel (SS) grinding chamber

0.2 μm filters

40 μm filter

Filling unit

Autoclave

Dry heat oven

Manufacturing

Zirconium beads were cleaned and rinsed using water for injections and then depyrogenised by dry heat (120 min at 260° C.). Water for injections was transferred into a SS container. Polysorbate 20 was added and dissolved by mixing. The solution was sterilized by filtration through a sterile 0.2 μm filter into a sterilized SS container. Paliperidone palmitate ester (sterile grade) as prepared in the previous examples was dispersed into the solution and mixed until homogeneous. The suspension was milled aseptically in the grinding chamber using Zirconium beads as grinding media until the required particle size was reached. The suspension was filtered aseptically through a 40 μm filter into a sterilized SS container

Water for injections was transferred into a SS container, citric acid monohydrate parenteral, disodium hydrogen phosphate anhydrous, sodium dihydrogen phosphate monohydrate, sodium hydroxide all use, polyethylene glycol 4000 were added and mixed until dissolved. This solution was sterilized by filtration through a sterile 0.2 μm filter and transferred aseptically into the suspension. The final suspension was mixed until homogeneous. The suspension was filled aseptically into sterile syringes. The target dose volume was between 0.25 ml and 1.50 ml depending on the dose needed.

TABLE 3

Dose volume	Target limit	lower limit	upper limit
0.25 ml-1.00 ml	identical to dose volume	target limit − (target limit × 0.05)	target limit × 1.05
1.25 ml-1.50 ml	identical to dose volume	target limit − (target limit × 0.025)	target limit × 1.025

Sterilization

All aseptic manipulations and sterilization processes were carried out according to FDA and European regulatory guidelines.

Apparatus

Sterilization was done by steam sterilization ($F_0 \geq 15$ of following equipment:

SS containers

Zirconium beads+grinding chamber

0.2 μm filters

40 μm filter

filling pump

Immediate Container

1 ml long transparent plastic (COC) syringe with luer lock.

rubber tip cap, FM257/2 dark grey

rubber plunger stopper, 1 ml long, 4023/50, Fluorotec B2-40

2.25 ml transparent plastic (COC) syringe with luer lock.

rubber tip cap, FM257/2 dark grey

rubber plunger stopper, 1-3 ml, 4023/50, Fluorotec B2-40

The empty syringes with pre-assembled tip-caps were sterilized by gamma-irradiation (dose ≥25 kGy). The rubber plunger stoppers were sterilized by means of steam sterilization ($F_0 \geq 1$□.

EXAMPLE 2

Evaluation of the Pharmacokinetic Profile of Glutcal Versus Deltoid Intramuscular Injections of Paliperidone Palmitate 100 mg Equivalent in Patients with Schizophrenia

This study was performed to characterize and compare the pharmacokinetic profile of paliperidone palmitate (formu-

lated as described above) following four intramuscular injections in the deltoid or gluteal muscle.

Method

In this multiple-dose, open-label, parallel-group study, patients with schizophrenia were randomized to receive four consecutive intramuscular injections (days 1, 8, 36 and 64) of paliperidone palmitate 100 mg-eq. administered into either the deltoid (n=24) or gluteal muscle (n=25). Plasma samples for pharmacokinetic analyses were collected. The total paliperidone concentration was calculated as the sum of both enantiomers.

Results

The median C_{max} for paliperidone was higher in the deltoid versus the gluteal muscle after the second (31.3 versus 24.1 ng/mL) and fourth (23.7 versus 22.3 ng/mL) injections. After four injections, median AUC_{∞} was similar for both injection sites; C_{max} and AUC_{τ} for paliperidone were 30% (90% CI=100.56%-168.93%) and 20% (90% CI=93.09%-154.69%) higher in deltoid versus gluteal muscle, respectively. Median T_{max} was similar between injection sites after the second (10 day versus 10 day) and fourth injections (5 versus 6.5 days). After four injections, the median peak-to-trough ratio was higher (2.3 versus 1.9), with a larger intersubject variability for deltoid versus gluteal injection. An increase in median predose plasma concentration between days 8, 36 and 64 for both sites suggested subjects were not completely at steady state after four injections. Relative exposure after the fourth injection was slightly lower than after the second injection in both the deltoid and gluteal muscle. Most commonly reported adverse events (combined injection sites) were orthostatic hypotension (24%), hypotension (14%), diastolic hypotension (12%) and injection site pain (14%). There were four serious adverse events (worsening of psychosis) that led to discontinuations. There were no deaths in the study. Paliperidone palmitate was well tolerated with more favorable local tolerability profile in the gluteal versus deltoid; mean injection site pain VSA score was 3.3 for gluteal versus 10.8 for deltoid muscle (day 1, 8 hours after injection.

Conclusion

Paliperidone palmitate 100 mg-eq. injections resulted in an increased AUC_{τ} higher C_{max}, greater FI, but similar T_{max} following four consecutive injections into the deltoid versus gluteal muscle. Paliperidone palmitate 100 mg-eq. was systemically and locally well tolerated in this study.

EXAMPLE 3

Assessment of the Dose Proportionality of Paliperidone Palmitate 25, 50, 100, and 150 mg eq. Following Administration in the Deltoid or Gluteal Muscles

This study evaluated dose proportionality of paliperidone palmitate injections when administered into either the gluteal or deltoid muscle.

Method

A single-dose, open label, parallel-group study of 201 randomized schizophrenia subjects was performed. The subjects were assigned into eight treatment groups: paliperidone palmitate 25 (n=48), 50 (n=50), 100 (n=51) or 150 (n=52) mg-eq. injected into either the deltoid or gluteal muscle. Serial plasma samples were collected for pharmacokinetic evaluation over 126-day period. The total paliperidone concentration was calculated as the sum of both enantiomers. Dose proportionality was assessed by linear regression model, for each injection site, with log-transformed dose-normalized AUC_{∞} and C_{max} as dependent variables and log-transformed dose as predictor, respectively of C_{max} and AUC_{∞} ratios of the enantiomers were documented.

Results

Slopes for log-transformed dose-normalized AUC_{∞} were not significantly different from zero for deltoid (slope −0.06; p=0.036) and gluteal injections (slope −0.02; p=0.760 indicating a dose-proportional increase in AUC_{∞}, T_{max} was comparable between doses but slightly earlier for deltoid (13-14 days) versus gluteal injections (13-17 days). Median C_{max} was higher with deltoid (range 5.3-11.0 ng/mL) versus gluteal (range 5.1-8.7 ng/mL) injections except for the 100 mg-eq. deltoid (slope −0.22, p=0.0062) and gluteal (slope −0.31; p<0.0001) injections, indicating a less than dose-proportional increase in C_{max}. Results of C_{max} and AUC were confirmed using pairwise comparisons. Plasma concentrations of (+)-enantiomer were consistently higher than (−)-enantiomer; (+)/(−) plasma concentrations ratio was approximately 2.4 shortly after administration and decreased to ~1.7 for both injection sites, independent of dose. After a single dose of paliperidone palmitate, subjects received concomitant oral antipsychotics. Treatment-emergent AEs (TEAs) included tachycardia (10%), headache (7%), schizophrenia (6%), insomnia (5%). Only 2% of subjects discontinued due to TEAs. No deaths were reported.

Conclusion

AUC_{∞} increased proportionality with increasing paliperidone palmitate doses (5-150 mg-eq.), regardless of gluteal or deltoid injection. Overall, deltoid injection was associated with a higher C_{max}(except for 100 mg-eq.) and slightly earlier T_{max} compared with gluteal injections.

EXAMPLE 4

Comparison of the PK Profile in the Deltoid to that in the Gluteal

The plasma concentration-time profile of paliperidone after single i.m. injection of the paliperidone palmitate formulation at 25-150 mg-eq. has been documented in several studies (Table 4). Details of how the comparison of injection sites study and the dose proportionality studies were performed are provided in Examples 2 and 3.

TABLE 4

Table of Clinical Studies Summarized

Study	Design/Treatment/PK Objective
PHASE 1 STUDIES IN SUBJECTS WITH SCHIZOPHRENIA	
R092670-INT-12 (dose-proportionality)	S.D., OL, parallel group/single i.m. injection of F011*, 25, 50, 100 or 150 mg eq./document PK of the F011* formulation at different doses, enantiomer disposition

TABLE 4-continued

Table of Clinical Studies Summarized

Study	Design/Treatment/PK Objective
	PHASE 1 STUDIES IN SUBJECTS WITH SCHIZOPHRENIA
R092670-USA-3	M.D., OL, randomized, parallel groups/2 i.m. injections of R092670 (F011*) 25 or 150 mg eq., gluteal or deltoid, separated by 1 week/ compare the PK after deltoid and gluteal injections, explore the relationship between R092670 PK parameters and CYP P450 genotypes
R092670-PSY-1001 (comparison of injection site)	M.D., OL, randomized, parallel groups/4 i.m. injections of R092670 (F013) 100 mg eq. in the gluteal or deltoid muscle (on Day 1, 8, 36 and 64)/compare the PK at steady state between deltoid and gluteal injection sites
R092670-PSY-1004 (dose-proportionality)	S.D., OL, randomized, parallel groups/single i.m. injection of R092670 (F013) 25, 50, 100 or 150 mg eq. in the gluteal or deltoid muscle/evaluate dose proportionality of F013 formulation over a dose range of 25-150 mg eq., compare the PK after deltoid and gluteal injections

S.D.: single dose; M.D.: multiple dose; OL: open-label; DB: double blind; PK: pharmacokinetic; PC: placebo-controlled; AC: active-controlled; pali ER: paliperidone extended release; pali IR: paliperidone immediate release F011*: Sterilized by gamma-irradiation. Otherwise, sterilized by aseptic crystallization.

The total exposure (AUC_∞) of paliperidone increased proportionally with dose after single-dose injections of 25 to 150 mg eq. paliperidone palmitate in both the deltoid and gluteal muscle. The increase in C_{max} was slightly less than dose proportional for both injections sites at doses greater than 50 mg eq. The apparent half-life (reflecting the absorption rate for this type of formulations) increased with dose from 25 days (median) after the 25 mg eq. dose to 40-49 days (median) after the 100 and 150 mg eq. dose, for both injection sites. The C_{max} of paliperidone was generally higher after single-dose injection of paliperidone palmitate in the deltoid muscle compared to the gluteal muscle (geometric mean ratio ranging from 108.75% to 164.85%) whereas this was much less pronounced for AUC_∞ (geometric mean ratio ranging from 103.00% to 117.83%). The median apparent half-life was comparable between injection sites.

EXAMPLE 5

Description of the PK Profile in the Gluteal After Multiple Administrations

Paliperidone palmitate is a long-acting i.m. injectable, intended to release over a period of 1 month. In order to attain this long injection interval, an ester of paliperidone was prepared that has a limited solubility in a physiological environment. The ester was subsequently formulated as an aqueous suspension for i.m. injection. The rate of dissolution is governed by the particle size distribution whereby it was experimentally determined that an optimal particle size range is contained within xx-yy microm (d_{50v}). In fact, the rate of dissolution (and thus the particle size distribution) fully determines the in vivo behaviour, as was nicely demonstrated in study PSY-1002. It was found that the median C_{max} increases and t_{max} shortens with decreasing particle size, which is consistent with the hypothesis that particle size is driving the release rate. The point estimates suggest that paliperidone exposure (AUC, C_{max}) after injection of paliperidone palmitate is similar between the to-be-marketed formulation F013 and formulation F011.

TABLE 5

Table of Clinical Studies Summarized in Module 2.7.2

Study	Design/Treatment/PK Objective
	PHASE 1 STUDIES IN SUBJECTS WITH SCHIZOPHRENIA
R092670-BEL-4 (pilot, dose-proportionality)	M.D., OL, sequential, parallel groups/4-6 monthly i.m. injections of F004, 50 mg eq. or 100 mg eq. or 150 mg eq./explore M.D. PK and dose-proportionality
R092670-BEL-7 (dosing regimen)	M.D., OL, parallel groups/F004 formulation: Panel I: 100 mg eq. i.m. followed by 3 monthly i.m. injections of 50 mg eq.; Panel II: 200 mg eq. i.m. followed by 3 monthly i.m. injections of 100 mg eq.; Panel III: 300 mg eq. i.m. followed by 3 monthly i.m. injections of 150 mg eq.; Panel IV: 50 mg eq. i.m. followed by 1 week later by 4 monthly i.m. injections of 50 mg eq.; Panel V: 150 mg eq. i.m. followed by 1 week later by 4 monthly i.m. injections of 150 mg eq./ explore the M.D. PK with various dosing regimens
R092670-INT-11 (compare F004 and F011)	M.D., DB, randomized, 4-group 2-way cross-over/4 monthly i.m. injections of F004 or F011*, 2 × 50 and 2 × 150 mg eq./compare PK of F004 and F011* formulations; compare S.D. and M.D. PK of both formulations
R092670-PSY-1002 (IVIVC)	S.D., OL, randomized, parallel groups/single i.m. injections of 1 mg paliperidone IR, followed by single i.m. injection of 50 mg eq. R092670: 1 of 4 F013 formulations with different particle sizes, or

TABLE 5-continued

Table of Clinical Studies Summarized in Module 2.7.2

Study	Design/Treatment/PK Objective
	PHASE 1 STUDIES IN SUBJECTS WITH SCHIZOPHRENIA
R092670-PSY-1001 (comparison of injection site)	F011 formulation with medium particle size/explore IVIVC of 4 F013 formulations, compare the PK of F011 and F013 formulations M.D., OL, randomized, parallel groups/4 i.m. injections of R092670 (F013) 100 mg eq. in the gluteal or deltoid muscle (on Day 1, 8, 36 and 64)/compare the PK at steady state between deltoid and gluteal injection sites

S.D.: single dose; M.D.: multiple dose; OL: open-label; DB: double blind; PK: pharmacokinetic; PC: placebo-controlled; AC: active-controlled; pali ER: paliperidone extended release; pali IR: paliperidone immediate release F011*: Sterilized by gamma-irradiation. Otherwise, sterilized by aseptic crystallization.

Pharmacokinetic theory also implies that for a formulation with such a long apparent half-life it takes 4-5 times this half-life for steady-state to be achieved. For individual patients, this means that following the first few injections, only subtherapeutic plasma concentrations are achieved. In order to overcome this problem, a loading dose regimen was developed (BEL-7), that was subsequently used in phase 2 and 3 of drug development. The dosing regimen consisting of two initial i.m. injections separated by one week followed by subsequent doses at monthly intervals resulted in a faster attainment of apparent steady state compared with a dosing regimen of one initial injection of twice the monthly dose followed by subsequent doses at monthly intervals. Somewhat higher peak-to-through fluctuations were observed with the first dosing regimen as compared with the latter one. The dosing regimen consisting of two initial i.m. injections separated by one week followed by subsequent doses at monthly intervals was selected for further studies and is also the recommended regimen for treatment.

EXAMPLE 6

Description of the Exposure Range Needed for Efficacy Using Invega Data

All antipsychotic drugs currently on the market have one feature in common: they antagonize the D_2 receptor at the level of the brain. It has been empirically derived and is currently widely excepted that 65-70% occupancy is needed for antipsychotics to show clinical efficacy (Farde et al.), i.e. improvement on the PANSS scale. A too high occupancy (80-85%) will typically increase the risk to develop EPS. In order to determine the central D_2 occupancy, PET trials in human healthy volunteers are typically performed. Two such studies have been done for paliperidone: SWE-1 and SIV-101, showing that the K_D^{app} for D_2 occupancy was ranging from 4.4 to 6.4 ng/mL. Using the 65-85% occupancy window, it can be calculated that the exposure range for efficacy without an increased risk to develop EPS as compared to placebo (<5% difference in probability) is contained in the window of 7.5-40 ng/mL.

In addition, based on the results of the phase 3 program of 6 mg paliperidone ER, in which plasma samples were collected at several time points, a plasma concentration of 7.5 ng/mL was identified as the cut-off value above which 90% of the plasma concentrations were observed. The risk to develop EPS was clearly higher for dose above 9 mg Invega. Calculating back, this roughly corresponds to an exposure level of 35-40 ng/mL at steady-state. This implies that there is ample evidence to support a target exposure efficacy range of 7.5-40 ng/mL. This should be the target exposure range for paliperidone after injection of the paliperidone palmitate formulation.

EXAMPLE 7

Optimal Way of Dosing

During the development of paliperidone palmitate, as the result of an extensive population PK analysis (refer to popPK report for paliperidone palmitate), several factors were found to slow down the release of paliperidone from the formulation, resulting in a slower build-up of plasma concentrations at the start of therapy and in more time required to reach steady-state. One factor was body mass index: the higher the BMI, the slower the dissolution (probably related to local physiological factors such as diminished blood flow at the site of injection); the other one being volume administered: the higher the volume injected, the slower the dissolution (probably related to the nonlinear relationship between surface area and volume). This has resulted in a lower than expected exposure using the originally proposed loading dose regimen, and the need to come up with an improved loading dose scheme for all patients irrespective of BMI in order to avoid drop-out due to lack of efficacy at the start of therapy. The aim was to get patients as quickly as possible above the 7.5 ng/mL, certainly after 1 week for all doses considered (25 mg-eq. and above).

Simulation scenarios with the statistically significant covariates from the population PK analysis revealed the following features about the paliperidone PK after injection of paliperidone palmitate:

- Compared to deltoid injections, repeated administration in the gluteal muscle resulted in a delayed time to achieve steady-state (~4 wk longer), but did not influence the overall exposure (in terms of steady-state concentrations) to paliperidone.
- Deltoid injections resulted in a faster rise in initial plasma concentrations, facilitating a rapid attainment of potential therapeutic plasma concentrations. The deltoid injection site is therefore recommended as the initiation site for dosing paliperidone palmitate.
- Higher doses, associated with larger injection volumes, increased the apparent half-life of paliperidone, which in turn increased the time to achieve steady-state.
- Needle length was an important variable for the absorption kinetics from the deltoid injection-site and it is recommended to use a longer 1.5-inch needle for deltoid administration in heavy subjects (≥90 kg). Simulations indicated that the use of a longer needle in the deltoid muscle for the heavy individuals might be associated with an initial faster release of paliperidone

into the systemic circulation, which could help overcome the slower absorption observed in heavier individuals described below.

The body size variable BMI was another important covariate for paliperidone palmitate. A slower rise in initial concentrations was observed in the obese population, which possibly occurred due to the reduced speed of initial influx from the injection site. Initiating the first two injections in the deltoid muscle and using a longer 1.5-inch needle for deltoid injection in heavy subjects can mitigate this effect. These observations are consistent with the expectation that in heavy subjects, administration into the adipose layer of the deltoid muscle can be avoided with the use of a longer injection needle.

Summarize what the optimized loading dose regimens would be here:

150 deltoid (day 1), 100 mg deltoid (day 8), then every 4 weeks maintenance (gluteal or deltoid) (PSY-3006, simulations—popPK report palmitate)

100 deltoid (day 1), 100 mg deltoid (day 8), then every 4 weeks maintenance (gluteal or deltoid) (simulations—popPK report palmitate, proposed for the label)

150 mg deltoid day 1, maintenance dose day 8 and then every 4 weeks (gluteal or deltoid) (PSY-3007)

EXAMPLE 8

Title of Study:

A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Dose-Response Study to Evaluate the Efficacy and Safety of 3 Fixed Doses (25 mg eq., 100 mg eq., and 150 mg eq.) of Paliperidone Palmitate in Subjects With Schizophrenia

Phase of Development:

Phase 3

Objectives:

The primary objectives of this study were to evaluate the efficacy and safety of 3 fixed doses of paliperidone palmitate administered intramuscularly (i.m.) after an initial dose of 150 mg equivalent (eq.) in the deltoid muscle followed by either deltoid or gluteal injections for a total of 13 weeks of treatment as compared with placebo in subjects with schizophrenia.

The secondary objectives were to:

Assess the benefits in personal and social functioning (key secondary endpoint) associated with the use of paliperidone palmitate compared with placebo;

Assess the global improvement in severity of illness associated with the use of paliperidone palmitate compared with placebo;

Assess the dose-response and exposure-response relationships of paliperidone palmitate.

Methods:

This was a randomized, double-blind, placebo-controlled, parallel-group, multicenter, dose-response study of men and women, 18 years of age and older, who had a Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) diagnosis of schizophrenia. The study included a screening period of up to 7 days and a 13-week double-blind treatment period. The screening period included a washout of disallowed psychotropic medications.

Subjects without source documentation of previous exposure to at least 2 doses of oral risperidone or paliperidone extended-release (ER), at least 1 dose of i.m. RISPERDAL® CONSTA® or paliperidone palmitate, or who were not currently receiving an antipsychotic medication were given 4 to 6 days of paliperidone ER 6 mg/day (or the option of oral risperidone 3 mg/day for subjects in Malaysia) for tolerability testing. Subjects who had source documentation of previous exposure to the above medications and were currently taking another antipsychotic regimen continued their current treatment through Day-1. At the beginning of the double-blind treatment period, subjects were randomly assigned in a 1:1:1:1 ratio to 1 of 4 treatment groups: placebo or paliperidone palmitate 25 mg eq., 100 mg eq., or 150 mg eq. Study medication was administered as 4 doses: an initial i.m. injection of 150 mg eq. of paliperidone palmitate or placebo followed by 3 fixed i.m. doses of placebo or paliperidone palmitate [25, 100, or 150 mg eq.] on Days 8, 36, and 64. The initial injection of study medication was given in the deltoid muscle. Subsequent injections were given either in the deltoid or gluteal muscle at the discretion of the investigator. Randomized subjects were to remain in the study for 28 days after the last injection on Day 64 with the end of study visit scheduled for Day 92 during the double-blind period. The entire study, including the screening period, lasted approximately 14 weeks. Samples for pharmacokinetic (PK) evaluation were collected on Day 1, prior to the first injection and on Days 2, 4, 6, 8, 15, 22, 36, 64 and 92. Efficacy and safety were evaluated regularly throughout the study. A pharmacogenomic blood sample (10 mL) was collected from subjects who gave separate written informed consent for this part of the study. Participation in the pharmacogenomic research was optional. Approximately 105 to 115 mL of whole blood was collected during the study.

Number of Subjects (Planned and Analyzed):

It was planned to include approximately 644 men and women in this study. A total of 652 eligible subjects from 72 centers in 8 countries were randomized and received at least 1 dose of double-blind study medication (safety analysis set); 636 subjects had both baseline and post baseline efficacy data (intent-to-treat analysis set).

Diagnosis and Main Criteria for Inclusion:

Male or female subjects ≥18 years of age who met the DSM-IV diagnostic criteria for schizophrenia for at least 1 year before screening, had a Positive and Negative Syndrome Scale (PANSS) total score at screening of between 70 and 120, inclusive, and at baseline of between 60 and 120, inclusive, and had a body mass index (BMI) of >17.0 kg/m^2 to <40 kg/m^2 were eligible.

Test Product, Dose and Mode of Administration, Batch No.:

Paliperidone ER was supplied as a 6-mg capsule-shaped tablet for the oral tolerability test (batch number 0617714/F40). Paliperidone palmitate was supplied as 25, 100, or 150 mg eq. injectable suspension (batch numbers 06K22/F13 and 07D23/F13). For the oral tolerability test, a 6-mg tablet of paliperidone ER (or the option of oral risperidone 3 mg/day for subjects in Malaysia) was administered daily for 4 to 6 days. On Day 1 of the double-blind treatment period, 150 mg eq. of paliperidone palmitate was injected in the deltoid muscle followed by 25, 100, or 150 mg eq. i.m. injections of paliperidone palmitate on Days 8, 36, and 64, injected into the deltoid or gluteal muscle at the investigator's discretion.

Reference Therapy, Dose and Mode of Administration, Batch No.:

Placebo was supplied as 20% Intralipid (200 mg/mL) injectable emulsion (batch numbers 06K14/F00 and 07F12/F00). An injection was given on Days 1, 8, 36 and 64.

Duration of Treatment:

The study consisted of a screening and washout phase of 7 days and a double-blind treatment period of 13 weeks, starting with the first injection in the deltoid muscle followed by a second injection 1 week later. All injections after Day 1 were given in either the deltoid or the gluteal muscle at the discretion of the investigator. Two subsequent injections were given at 4-week intervals.

Criteria for Evaluation:

Pharmacokinetic Evaluations:

A sparse blood sampling procedure was followed to study the paliperidone concentration-time profiles. Paliperidone plasma concentration-time data were subject to population PK analysis using nonlinear mixed-effects modeling, and details are described in a separate report.

Efficacy Evaluations/Criteria:

The primary endpoint was the change in the PANSS total score from baseline (i.e., the start of double-blind treatment, Day 1) to the end of the double-blind treatment period (i.e., Day 92 or the last post baseline assessment). The key secondary efficacy endpoint was the change in the Personal and Social Performance Scale (PSP) from baseline to the end of the double-blind treatment period. The other secondary efficacy endpoint was the change in the Clinical Global Impression-Severity (CGI-S) scores from baseline to the end of the double-blind treatment period. Other endpoints included the change from baseline in subject ratings of sleep quality and daytime drowsiness using a visual analogue scale (VAS), the onset of therapeutic effect, responder rate, and the change from baseline to end point in PANSS subscales and Marder factors.

Safety Evaluations:

Safety was monitored by the evaluation of adverse events, extrapyramidal symptom (EPS) rating scales (Abnormal Involuntary Movement Scale [AIMS], Barnes Akathisia Rating Scale [BARS], Simpson and Angus Rating Scale [SAS]) scores, clinical laboratory test results, vital signs measurements, electrocardiograms (ECGs), and physical examination findings. In addition, the tolerability of injections was assessed; the investigators evaluated injection sites and the subjects assessed injection pain.

Statistical Methods:

All randomized subjects who received at least 1 dose of double-blind study drug and had both baseline and at least one post baseline efficacy measurement (PANSS, PSP, or CGI-S) during the double-blind treatment period were included in the intent-to-treat efficacy analyses. The overall type I error rate for testing all paliperidone palmitate doses versus placebo for both the primary endpoint (change in PANSS total score at end point) and the key secondary efficacy endpoint (change in PSP total score at end point) was controlled at the 2-sided 0.05 significance level. The 2 families of hypotheses (in each family, 3 comparisons for each of the paliperidone palmitate doses versus placebo) were tested using a parallel gatekeeping procedure that adjusts for multiplicity using Dunnett's method in each family of hypotheses and using Bonferroni's inequality between different families of hypotheses. This procedure is referred to as the Dunnett-Bonferroni-based parallel gatekeeping procedure.

The change from baseline in PANSS total score at each visit and at end point was analyzed using an analysis of covariance (ANCOVA) model. The last observation carried forward (LOCF) method was used. The model included treatment and country as factors and baseline PANSS total score as a covariate. Treatment effect was based on the difference in least-squares mean change. Dunnett's test was used to adjust for multiple comparisons of the 3 paliperidone palmitate dosages versus placebo. Unadjusted 2-sided 95% confidence intervals were presented for the difference in least-squares mean change of each paliperidone palmitate dosage group compared with placebo. Treatment-by-country and treatment-by-baseline PANSS total score interactions were explored using the same ANCOVA model as the one for the analysis of the primary endpoint. If either term was statistically significant at the predefined 2-sided significance level of 0.10, further evaluations of the effect of other covariates were to be performed to assess the nature of the interaction and identify possible causes. In addition, to address the dose-response relationship and to facilitate the discussion of dosage selection, an analysis to compare the 3 active paliperidone palmitate dosages with each other was performed without adjustment for multiple comparisons.

The analysis of the key secondary endpoint, change in PSP score at end point, was conducted by means of an ANCOVA model with treatment and country as factors and the baseline score as the covariate. The Dunnett-Bonferroni-based parallel gatekeeping approach was used to adjust for multiple testing.

Between-group comparisons of CGI-S were performed by using an ANCOVA model on the ranks of change from baseline, with treatment and country as factors and the baseline score as the covariate.

Change from baseline over time (observed case) in the PANSS total score was explored using mixed effects linear models for repeated measures with time, treatment, country, and treatment-by-time as factors and baseline score as a covariate.

The number and percentage of subjects with treatment-emergent adverse events were summarized. Adverse events of potential clinical interest were summarized separately, including events related to EPS or changes in serum glucose or prolactin levels.

Changes from baseline in clinical laboratory tests, vital sign measurements, ECGs, body weight, BMI, and EPS scale scores were summarized by treatment group. Prolactin levels were summarized by sex. Subjects with potentially abnormal values or changes in clinical laboratory tests, vital signs, orthostatic parameters, and ECG parameters were summarized based on predefined criteria. Frequency distributions were presented for the investigator's evaluation of the injection site, and descriptive statistics were presented for VAS scores corresponding to the subject's evaluation of injection pain.

Results:

The majority of subjects in the paliperidone palmitate treatment groups (56%-61%) received all 4 injections compared with 48% of the placebo-treated subjects. Completion rates were also higher for the paliperidone palmitate groups (52%-55%) than for the placebo group (43%). More subjects were discontinued for lack of efficacy in the placebo group (27%) compared with the paliperidone palmitate groups (14%-19%).

Demographic and Baseline Characteristics:

The double-blind treatment groups were well matched with respect to demographic and baseline disease characteristics and psychiatric history. The 636 subjects who comprised the intent-to-treat analysis set were mainly male (67%), racially diverse (54% White, 30% Black, 14% Asian, 1% other races), and predominately between the ages of 26 and 50 years (75%). Most subjects had a primary diagnosis of paranoid schizophrenia (88%), and were highly symptomatic as indicated by a mean PANSS total score of 87.1 at baseline. There were notable differences between countries with respect to BMI and gender, with subjects enrolled at centers in the U.S. being more likely to be male and obese (i.e., BMI≥30 kg/m^2) than those from centers in other countries.

Pharmacokinetics:

A total of 488 subjects who were randomly assigned to receive paliperidone palmitate treatment had scheduled pharmacokinetic blood samples taken over the course of the study. The median paliperidone predose concentration for the 25 mg eq. treatment group was highest on Day 8, which is the result of the initial 150 mg eq. dose on Day 1. After

Day 8, paliperidone concentrations decreased and seemed to reach steady state levels on Day 92 based on visual inspection. The median paliperidone predose concentration for the 100 mg eq. treatment group remained in the same range from Day 8 onwards. The median predose concentration for the 150 mg eq. treatment group seemed to increase up to the last study day, Day 92. The median paliperidone plasma concentrations on Day 8 were lower in subjects with high BMI (≥25 to <30 kg/m^2 and ≥30 kg/m^2; overweight/obese) compared to subjects with low BMI (<25 kg/m^2) for the 3 dose groups. After Day 8, no consistent trends were observed for the 3 paliperidone palmitate dose groups with respect to paliperidone plasma concentrations as a function of baseline BMI classification.

The mean and median paliperidone plasma concentrations on Day 64 for the 100 mg eq. treatment group were approximately 2-fold higher than those for the 25 mg eq. treatment group. Thus, the PK profile for the 25 mg eq. and 100 mg eq. dose groups appeared to be less than dose proportional, which is the result of the initial paliperidone palmitate 150 mg eq. injection on Day 1 in all active treatment groups. The mean and median paliperidone plasma concentrations on Day 64 for the 100 mg eq. dose were apparently dose proportional compared to the 150 mg eq. dose. A high inter-subject variability was observed in the paliperidone plasma concentrations on Days 1 and 2 with a % CV of 118.9% (Day 1) and 153.1% (Day 2). After Day 2, the inter-subject variability decreased and the % CV ranged from 50.4 to 83.4%.

Primary Efficacy Analysis:

Adult subjects with schizophrenia achieved statistically significant improvements in the PANSS total score (primary efficacy endpoint) with all 3 doses of paliperidone palmitate compared to placebo (25 mg eq.: p=0.034; 100 mg eq.: p<0.001; 150 mg eq.: p<0.001) based on the intent-to-treat LOCF analysis and the Dunnett's test to control for multiplicity.

exploratory analysis additionally provided no statistical evidence for a BMI effect on treatment.

All 3 paliperidone palmitate dose groups showed a statistically significant improvement over placebo in the change in PANSS total score as of Day 22 and at every subsequent time point, and as early as Day 8 in the paliperidone palmitate 25 mg eq. and 150 mg eq. groups.

The mean improvements in the PSP score from baseline to end point, the key secondary efficacy outcome measure, showed a dose response among the 3 paliperidone palmitate groups (25 mg eq.: 2.9; 100 mg eq.: 6.1; 150 mg eq.: 8.3); all were numerically higher than the mean improvement in the PSP score seen in the placebo group (1.7). Based on the intent-to-treat LOCF analysis of this key secondary efficacy variable, using the Dunnett-Bonferroni-based parallel gatekeeping procedure to adjust for multiplicity, the improvement in the paliperidone palmitate 100 and 150 mg eq. treatment groups reached statistical significance (100 mg eq.: p=0.007; 150 mg eq.: p<0.001) when compared with the placebo group.

The paliperidone palmitate 100 mg eq. and 150 mg eq. groups were statistically significantly superior to placebo in improving the CGI-S scores from baseline to end point (LOCF) (without multiplicity adjustment, 100 mg eq.: p=0.005; 150 mg eq.: p<0.001). Significantly more subjects treated with paliperidone palmitate 25 mg eq. (33.5%; p=0.007), 100 mg eq. (41.0%; p<0.001), and 150 mg eq. (40.0%, p<0.001) achieved responder status (30% or larger decrease on PANSS total scores) than with placebo (20.0%).

Based on the intent-to-treat LOCF analysis of the change from baseline to end point without statistical adjustment for multiplicity, the paliperidone palmitate 100 and 150 mg eq. groups were statistically significantly superior to the placebo group for all 5 PANSS Marder factors (p<0.010). The improvements in both negative symptoms and disorganized thoughts factor scores were statistically significantly greater in the paliperidone palmitate 25 mg eq. group compared with placebo (p=0.032).

Positive and Negative Syndrome Scale for Schizophrenia (PANSS) Total Score - Change from Baseline to End Point-LOCF with the Dunnett-Bonferroni-Based Parallel Gatekeeping Procedure (Study R092670-PSY-3007: Intent-to-Treat Analysis Set)

	Placebo (N = 160)	R092670 25 mg eq. (N = 155)	R092670 100 mg eq. (N = 161)	R092670 150 mg eq. (N = 160)
Baseline Mean (SD)	86.8 (10.31)	86.9 (11.99)	86.2 (10.77)	88.4 (11.70)
End point Mean (SD)	83.9 (21.44)	78.8 (19.88)	74.6 (18.06)	75.2 (18.59)
Change from Baseline				
Mean (SD)	−2.9 (19.26)	−8.0 (19.90)	−11.6 (17.63)	−13.2 (18.48)
P-value (minus Placebo)[a]		0.034	<0.001	<0.001
Diff of LS Means (SE)		−5.1 (2.01)	−8.7 (2.00)	−9.8 (2.00)

[a]Based on analysis of covariance (ANCOVA) model with treatment (Placebo, R092670 25 mg eq., R092670 100 mg eq., R092670 150 mg eq.) and country as factors, and baseline value as a covariate. P-values were adjusted for multiplicity for comparison with placebo using Dunnett's test.
Note:
Negative change in score indicates improvement.

Other Efficacy Results:

There was a dose-response pattern with respect to the primary efficacy variable, with the mean decreases (improvement) in the PANSS total score at end point (LOCF).

Prespecified treatment-by-country and treatment-by-baseline PANSS total score interactions in the primary efficacy model were not statistically significant at the 0.10 level. An

Based on the intent-to-treat LOCF analysis using an ANCOVA model with no adjustment for multiplicity, the mean improvement in sleep quality in the paliperidone palmitate 100 mg eq. and 150 mg eq. groups were statistically significant (p<0.001 and p=0.026, respectively) when compared with placebo. The mean changes in daytime drowsiness in the paliperidone palmitate treatment groups were not statistically significantly different from that in the

placebo group (25 mg eq.: p=0.541; 100 mg eq.: p=0.340; 150 mg eq.: p=0.261).

Safety Results:

Paliperidone palmitate, injected at a dose of 150 mg eq. into the deltoid muscle followed by 3 i.m. injections at fixed doses of 25 mg eq., 100 mg eq., or 150 mg eq. on Days 8, 36, and 64, was generally well tolerated by adult subjects with schizophrenia during this 13-week study. Overall, the safety and tolerability results were consistent with previous clinical studies involving paliperidone palmitate, and no new safety signals were detected.

The overall summary of treatment-emergent adverse events is given below.

Overall Summary of Treatment-Emergent Adverse Events
(Study R092670-PSY-3007: Safety Analysis Set)

	Placebo (N = 164) n (%)	R092670 25 mg eq. (N = 160) n (%)	R092670 100 mg eq. (N = 165) n (%)	R092670 150 mg eq. (N = 163) n (%)	Total (N = 652) n (%)
TEAE	107 (65.2)	101 (63.1)	99 (60.0)	103 (63.2)	410 (62.9)
Possibly related TEAE[a]	47 (28.7)	45 (28.1)	49 (29.7)	51 (31.3)	192 (29.4)
TEAE leading to death	0	0	0	1 (0.6)	1 (0.2)
1 or more serious TEAE	23 (14.0)	15 (9.4)	22 (13.3)	13 (8.0)	73 (11.2)
TEAE leading to permanent stop	11 (6.7)	10 (6.3)	10 (6.1)	13 (8.0)	44 (6.7)

[a]Study drug relationships of possible, probable, and very likely are included in this category.
Adverse events are coded using MedDRA version 10.1

There was 1 death in a subject in the paliperidone palmitate 150 mg eq. group after withdrawal from the study due to an adverse event (cerebrovascular accident) that began during the study. This subject received 2 injections of study medication, with the last injection administered approximately 2 weeks before the subject died. While this event was assessed as doubtfully related to study treatment by the investigator, an unblinded review by the sponsor assessed this event to be possibly related to study treatment.

The number of subjects who experienced treatment-emergent serious adverse events was higher in the placebo group than in any of the paliperidone palmitate groups (see table above). Most serious adverse events in all treatment groups were psychiatric disorders (e.g., schizophrenia, psychotic disorder) that were likely the result of the natural course of the underlying schizophrenia. Adverse events leading to study discontinuation occurred at a similar low incidence across treatment groups.

Common treatment-emergent adverse events (≥2% of subjects in any treatment group) that occurred more frequently in the total paliperidone palmitate group (all 3 active dose groups combined) than in the placebo-treated subjects (i.e., ≥1% difference between the combined paliperidone palmitate group and the placebo group) were: injection site pain, dizziness, sedation, pain in extremity, and myalgia. An examination of treatment-emergent adverse events of potential clinical importance revealed no reports of seizure or convulsion, tardive dyskinesia, dermatologic events, neuroleptic malignant syndrome, hyperthermia, anaphylactic reaction, rhabdomyolysis, syndrome of inappropriate secretion of antidiuretic hormone, ventricular tachycardia, ventricular fibrillation, or torsades de pointes.

In general, the type and incidence of treatment-emergent adverse events did not differ as a function of baseline BMI categories (normal: <25 kg/m^2; overweight: ≥25 to <30 kg/m^2; obese: ≥30 kg/m^2).

The incidence of treatment-emergent EPS-related adverse events was low and comparable to placebo. Akathisia was the most frequently reported EPS-related adverse event (4.9% for the placebo group and 1.3%, 4.8%, 5.5% for the paliperidone palmitate 25, 100, and 150 mg eq. groups, respectively). None of the EPS-related adverse events reported in subjects receiving paliperidone palmitate were serious or treatment limiting, and only 1 was severe (musculoskeletal stiffness). Results of EPS rating scales and use of anti-EPS medication were consistent in indicating that paliperidone palmitate was associated with a low incidence of EPS.

No clinically relevant mean changes from baseline to end point in supine or standing pulse rates were apparent for any of the paliperidone palmitate doses. A similar, low percentage of subjects had pulse rate of ≥100 bpm with an increase of ≥15 bpm in the placebo and paliperidone palmitate groups (6% to 11% for standing measurements; 2% to 5% for supine measurements).

Assessment of ECG data did not demonstrate evidence of clinically significant QTc prolongation with paliperidone palmitate at doses up to 150 mg eq. No subject had a maximum QTcLD value >480 ms or a maximal change in QTcLD >60 ms during the study.

The increases in body weight with paliperidone palmitate over the 13-week double-blind treatment period were modest in a dose-related manner, averaging 0.4, 0.7, and 1.4 kg for the 25 mg eq., 100 mg eq., and 150 mg eq. groups, respectively (−0.2 kg for placebo); corresponding mean changes in BMI from baseline to end point were 0.1, 0.3, and 0.5 kg/m^2, respectively (−0.1 kg/m^2 for placebo). A clinically relevant weight increase of at least 7% relative to baseline was seen in 13% of subjects receiving the highest dose of paliperidone palmitate (compared with 5% for placebo).

Consistent with the known pharmacology of paliperidone, increases in prolactin levels were observed with greater frequency in subjects who received paliperidone palmitate, with the largest increase seen in the 150 mg eq. group. Overall, there was a low incidence of potentially prolactin-related adverse events, despite the known propensity of paliperidone palmitate to increase serum prolactin levels. This suggests that the clinical importance of this increase in serum prolactin levels is of questionable clinical significance.

Based on mean changes from baseline to end point and the occurrence of treatment-emergent markedly abnormal laboratory test values and adverse events related to abnormal laboratory analyte findings, except for prolactin, the effects

of paliperidone palmitate on the results of chemistry and hematology laboratory tests (including liver and renal function tests, serum lipid levels, and glucose levels) did not show clinically relevant differences from those of placebo.

Local injection site tolerability was good. Occurrences of induration, redness, or swelling as assessed by blinded study personnel were infrequent, generally mild, decreasing over time, and similar in incidence for the paliperidone palmitate and placebo groups. Investigator ratings of injection pain were similar for the placebo and paliperidone palmitate groups.

Study Limitations:

This study investigated the efficacy and safety of paliperidone palmitate for acute treatment of schizophrenia over 13 weeks and does not provide information on longer term treatment. The study was not designed to detect differences between doses of paliperidone palmitate; thus, dose-related trends in efficacy and safety can only be described descriptively. The study was also not designed to demonstrate efficacy for specific subgroups of subjects, such as those from a particular country. An independent, centralized blinded rating service was used for performing all ratings of PANSS, PSP and CGI-S for all subjects enrolled at U.S. sites. The investigators at these sites did not complete any of the ratings, which would have provided a reference for ratings provided by the rating service. Thus, data from this study cannot be used to fully evaluate the utility of using blinded independent raters for detecting treatment differences.

Conclusion:

All 3 doses of paliperidone palmitate tested in this study—25, 100, and 150 mg eq.—were efficacious in adult subjects with schizophrenia who were experiencing acutely exacerbated schizophrenia. Specifically, the results of the primary efficacy endpoint (change from baseline to end point in PANSS total score) demonstrated statistical superiority of paliperidone palmitate 25 mg eq., 100 mg eq., and 150 mg eq. over placebo. Significantly greater improvement in subjects' personal and social functioning (as measured by the PSP score) was also seen for the paliperidone palmitate 100 mg eq. and 150 mg eq. doses compared with placebo, and global improvement was validated by a favorable and statistically significant CGI-S change for these 2 dose groups. There was a dose response in the primary and secondary efficacy endpoints (PANSS, PSP, and CGI-S). All 3 doses of paliperidone palmitate, including the highest dose of 150 mg eq., were well tolerated, suggesting a positive benefit-risk ratio across the dose range currently studied. No new safety signal was detected.

FIGURES

FIGS. **1-3** graphically presents the observed versus population pharmacokinetics model simulation for plasma paliperidone concentrations. The line indicates the median values calculated from population pharmacokinetic simulation. The shading indicates 90% prediction interval representing the between and within subject, variability obtained using the population pharmacokinetic simulation. The circles indicate observed plasma paliperidone concentrations. The arrows indicate the days when paliperidone palmitate injection was given. As is apparent from the Figures the plasma profiles provided by initiating paliperidone with 150 mg eq. followed by a subsequent dose of 100 or 150 for days 1-36 provide a rapid rise to a therapeutic dose levels. Most preferably the dosing of paliperidone to patients should be maintained within ±25%, preferably 20% of the median plasma concentrations provided in these figures for days 1-36. For patients whose dosing continues at 100 mg eq. the preferably the dosing of paliperidone to patients should be maintained within ±25%, preferably 20% of the median plasma concentrations provided in FIG. **2** for days 1-64. For patients whose dosing continues at 150 mg eq. the preferably the dosing of paliperidone to patients should be maintained within ±25%, preferably 20% of the median plasma concentrations provided in FIG. **3** for days 1-64.

We claim:

1. A dosing regimen for administering paliperidone palmitate to a psychiatric patient in need of treatment for schizophrenia, schizoaffective disorder, or schizophreniform disorder comprising

(1) administering intramuscularly in the deltoid of a patient in need of treatment a first loading dose of about 150 mg-eq. of paliperidone as paliperidone palmitate formulated in a sustained release formulation on the first day of treatment;

(2) administering intramuscularly in the deltoid muscle of the patient in need of treatment a second loading dose of about 100 mg-eq. of paliperidone as paliperidone palmitate formulated in a sustained release formulation on the 6^{th} to about 10th day of treatment; and

(3) administering intramuscularly in the deltoid or gluteal muscle of the patient in need of treatment a first maintenance dose of about 25 mg-eq. to about 150 mg-eq. of paliperidone as paliperidone palmitate in a sustained release formulation a month (±7 days) after the second loading dose.

2. The dosing regimen of claim **1** wherein after administration of the first maintenance dose, subsequent maintenance doses of from about 25 mg-eq. to 150 mg-eq. are administered in the deltoid or gluteal muscle of the psychiatric patient in need of treatment at monthly (±7 days) intervals.

3. The dosing regimen of claim **1** wherein the sustained release formulation is an aqueous nanoparticle suspension.

4. A dosing regimen for administering paliperidone palmitate to a psychiatric patient in need of treatment for psychotic disorder comprising

(a) administering intramuscularly in the deltoid of a patient in need of treatment a first loading dose of about 150 mg-eq. of paliperidone as paliperidone palmitate formulated in a sustained release formulation on the first day of treatment;

(b) administering intramuscularly in the deltoid muscle of the patient in need of treatment a second loading dose of about 100 mg-eq. of paliperidone as paliperidone palmitate formulated in a sustained release formulation on the eighth day of treatment; and

(c) administering intramuscularly in the deltoid or gluteal muscle of the patient in need of treatment a first maintenance dose of about 25 mg-eq. to about 150 mg-eq. of paliperidone as paliperidone palmitate in a sustained release formulation a month (±7 days) after the second loading dose.

5. The dosing regimen of claim **4** wherein the sustained release formulation is an aqueous nanoparticle suspension.

6. The dosing regimen of claim **4** wherein the psychiatric patient is in need of treatment for psychotic disorder wherein the psychotic disorder is schizophrenia.

7. The dosing regimen of claim **4** wherein the psychiatric patient is in need of treatment for a psychotic disorder wherein the psychotic disorder is schizoaffective disorder.

8. A dosing regimen for administering paliperidone palmitate to a renally impaired psychiatric patient in need of

treatment for schizophrenia, schizoaffective disorder, or schizophreniform disorder comprising

(a) administering intramuscularly in the deltoid of a renally impaired psychiatric patient in need of treatment a first loading dose of from about 75 mg-eq. of paliperidone as paliperidone palmitate formulated in a sustained release formulation on the first day of treatment;

(b) administering intramuscularly in the deltoid muscle of the patient in need of treatment a second loading dose of from about 75 mg-eq. of paliperidone as paliperidone palmitate formulated in a sustained release formulation on the 6^{th} to about 10th day of treatment; and

(c) administering intramuscularly in the deltoid or gluteal muscle of the patient in need of treatment a first maintenance dose of about 25 mg-eq. to about 75 mg-eq. of paliperidone as paliperidone palmitate in a sustained release formulation a month (±7 days) after the second loading dose.

9. The dosing regimen of claim **8** wherein after the first maintenance dose, subsequent maintenance doses of from about 25 mg-eg. to 150 mg-eg. are administered in the deltoid or gluteal muscle of the psychiatric patient in need of treatment of monthly (±7) intervals.

10. The dosing regimen of claim **8** wherein the sustained release formulation is an aqueous nanoparticle suspension.

11. A dosing regimen for administering paliperidone palmitate to a renally impaired psychiatric patient in need of treatment for psychotic disorder comprising

(a) administering intramuscularly in the deltoid of a renally impaired psychiatric patient in need of treatment a first loading dose of from about 75 mg-eq. of paliperidone as paliperidone palmitate formulated in a sustained release formulation on the first day of treatment;

(b) administering intramuscularly in the deltoid muscle of the patient in need of treatment a second loading dose of from about 75 mg-eq. of paliperidone as paliperidone palmitate formulated in a sustained release formulation on the eighth day of treatment; and

(c) administering intramuscularly in the deltoid or gluteal muscle of the patient in need of treatment a first maintenance dose of about 25 mg-eq. to about 50 mg-eq. of paliperidone as paliperidone palmitate in a sustained release formulation a month (±7 days) after the second loading dose.

12. The dosing regimen of claim **11** wherein the sustained release formulation is an aqueous nanoparticle suspension.

13. The dosing regimen of claim **11** wherein the psychiatric patient is in need of treatment for of a psychotic disorder wherein the psychotic disorder is schizophrenia.

14. The dosing regimen of claim **11** wherein the psychiatric patient is in need of treatment for a psychotic disorder wherein the psychotic disorder is schizoaffective disorder.

15. The dosing regimen of claim **4** wherein after administration of the first maintenance dose, subsequent maintenance doses of from about 25 mg-eq. to 150 mg-eq. are administered in the deltoid or gluteal muscle of the psychiatric patient in need of treatment at monthly (±7 days) intervals.

16. The dosing regimen of claim **11** wherein after administration of the first maintenance dose, subsequent maintenance doses of from about 25 mg-eq. to 150 mg-eq. are administered in the deltoid or gluteal muscle of the psychiatric patient in need of treatment at monthly (±7 days) intervals.

17. The dosing regimen of claim **1**, **4**, **8** or **11** wherein the formulation is an aqueous nanoparticle suspension comprises

(a) from 3 to 20% (w/v) of the paliperidone palmitate having an average particle size (d50) of from about 1600 nm to about 900 nm;

(b) from 0.5 to 3% (w/v) of a wetting agent wherein the wetting agent is polysorbate 20;

(c) one or more buffering agents sufficient to render the composition neutral to very slightly basic (pH 8.5);

(d) from 0.5 to 3% (w/v) of a suspending agent wherein the suspending agent is polyethylene glycol 4000; and

(e) up to 2% (w/v) preservatives; and

(f) water q.s. ad 100%.

18. The dosage regimen of claim **17** wherein the concentration of paliperidone palmitate is 156 mg/ml in the aqueous nanoparticle suspension.

19. The dosing regimen of claims **1**, **4**, **8** or **11** wherein the sustained release depot formulation is an aqueous nanoparticle suspension consists essentially of

(a) 156 mg/ml of the paliperidone palmitate having an average particle size (d50) of from about 1600 nm to about 900 nm;

(b) 12 mg/ml of polysorbate 20;

(c) one or more buffering agents sufficient to render the composition neutral to very slightly basic (pH 8.5);

(d) 30 mg/ml of a suspending agent wherein the suspending agent is polyethylene glycol 4000; and

(f) water q.s. ad 100%.

20. The dosage regimen of claim **19** wherein in the buffering agents contained in the aqueous nanoparticle suspension are citric acid monohydrate, disodium hydrogen phosphate anhydrous, sodium dihydrogen phosphate monohydrate, sodium hydroxide.

21. The dosage regimen of claim **19** wherein in the pH of the aqueous nanoparticle suspension is in the range of pH 7 to 7.5.

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CERTIFICATE OF COMPLIANCE WITH TYPE-VOLUME LIMITATION

This brief complies with the type-volume limitations of the Federal Rules of Appellate Procedure and the Rules of this Court. According to the system used to prepare it, the brief contains 13,842 words.

/s/ *John C. O'Quinn*

CERTIFICATE OF COMPLIANCE WITH FED. CIR. R. 25.1

90 unique words are marked confidential in the confidential version of this brief and redacted in the non-confidential version. Appellants are filing a contemporaneous motion under Rule 25.1(d)(3).

/s/ *John C. O'Quinn*

CERTIFICATE OF SERVICE

On May 13, 2022, the non-confidential version of this brief was submitted to the Court by CM/ECF and thereby served on all parties, and the confidential version was served on the following counsel at the e-mail addresses below, under the parties' agreement to accept electronic service of confidential materials.

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